Zinc and infection: a review

LUIS E. CUEVAS & AI KOYANAGI

Liverpool School of Tropical Medicine, Liverpool, UK

(Accepted June 2005)

Abstract  Dietary zinc deficiency is widespread in developing countries and is often aggravated by intercurrent acute and chronic infections. Recent studies have demonstrated that zinc supplementation can significantly reduce the morbidity and mortality of apparently well-nourished children and shorten the time to recovery from acute infectious diseases. This review summarises current knowledge of the role of zinc in childhood diarrhoea, acute respiratory infections and malaria, and its potential role in diseases associated with impaired cellular immunity, namely tuberculosis, lepromatous leprosy and leishmaniasis, and explores avenues for future research.

Introduction

Dietary zinc deficiency is widespread in developing countries and is often aggravated by intercurrent acute and chronic infections. Recent studies have demonstrated that zinc supplementation of apparently well-nourished children can significantly reduce morbidity and mortality and shorten the time to recovery from common infectious diseases. Zinc is a key micronutrient that is present in all organs, tissues and body fluids. After iron, it is the second most abundant trace element in the body and mediates a wide variety of physiological functions. It is a necessary component of numerous metalloproteins, including those important for DNA replication and cell division, and is crucial for maintaining immunological integrity, predominantly cellular immunity and antioxidant activity. Because of its role in maintaining cell integrity and immunity, it is considered to play a key role in cells that have a rapid turnover and a critical role in the control and prevention of infections. Despite these functions, the body does not store zinc and requires a constant dietary intake. Zinc is more abundant and easily absorbed from red meat and animal proteins, but can also be obtained from seafood, dairy products, cereals and nuts. Most vegetables, however, are not good sources of zinc owing to the presence of phytate, a component of plants that chelates zinc and prevents its absorption. Diets that are low in animal protein and rich in phytate thus contribute to the high prevalence of zinc deficiency in developing countries.

This review describes the effect that zinc deficiency and replenishment has on common acute infectious diseases in developing countries, namely acute respiratory infections, diarrhoea and malaria, and its potential role in diseases associated with impaired cellular immunity, namely tuberculosis, lepromatous leprosy and leishmaniasis.

Clinical Symptoms Associated with Zinc Deficiency

The extreme clinical spectrum of zinc deficiency is illustrated by the rare congenital...
disorder, acrodermatitis enteropathica, that results from an inability to absorb zinc. The main characteristics of this syndrome are dermatitis, intractable diarrhoea, mood and behavioural changes, growth retardation, anorexia, recurrent bacterial and fungal infections and pneumonia.\textsuperscript{9,10} Zinc supplementation readily improves the symptoms.

**Zinc and Diarrhoea**

The effect of zinc on diarrhoea might be related to its role in water and electrolyte transport, intestinal permeability,\textsuperscript{11–14} enzyme functions of the enterocyte,\textsuperscript{15} enhanced intestinal tissue repair\textsuperscript{16,17} or enhanced local immunity restricting bacterial overgrowth and early pathogen clearance.\textsuperscript{5} More than one of these mechanisms are likely to be involved at any one time.

Children with acute and persistent diarrhoea often have low serum zinc concentrations at presentation\textsuperscript{18–20} and serum levels correlate with the duration of the episode.\textsuperscript{21} However, it is difficult to distinguish whether low levels precede the episode, exacerbating the child's susceptibility to infection, or result from increased losses and organ redistribution during the acute episode, as zinc levels rapidly change during the acute phase of infection. Cohort studies of normal and malnourished children have demonstrated that low zinc concentrations in asymptomatic children are associated with a higher incidence and severity of diarrhoea during the following months.\textsuperscript{22} These findings led to clinical trials in Asia and Africa that consistently demonstrated that supplementing apparently healthy or stunted children reduces the incidence and severity of diarrhoea.\textsuperscript{5,23–25} This effect occurs in all children since all but one study in Bangladesh observed that the reduction in morbidity was independent of zinc concentration levels on enrolment.\textsuperscript{26}

Besides its role in the prevention of diarrhoea, zinc also has a therapeutic role in treating acute episodes. Supplementation trials using zinc tablets or syrup as an adjunct to oral rehydration solutions (ORS) resulted in a reduction of at least 20\% in the duration of the acute episode, lower ORS requirements, lower stool output\textsuperscript{27} and a 43–47\% reduction in the risk of developing prolonged diarrhoea beyond the 7th day of illness.\textsuperscript{28} These effects seem to occur regardless of the nutritional status of the child or the presence of viruses or bacteria in the stools.\textsuperscript{29,30} Although it would appear ideal to incorporate zinc into ORS, there have been only two trials to assess the efficacy of this method.\textsuperscript{31,32} In both studies, there was less or no benefit compared with providing the supplements separately and presently this approach is not recommended. Zinc supplements for acute diarrhoea can therefore be given as gluconate, sulphate or acetate, either in tablet or syrup form as clinical trials have not observed differences between these presentations.

In addition to its effect on acute diarrhoea, zinc also reduces the risk of developing persistent diarrhoea and reduces treatment failure in children who already have persistent diarrhoea which has a high mortality in developing countries.\textsuperscript{33–37} There is thus evidence that zinc supplementation is an effective agent in treating and preventing diarrhoea. A summary of the main findings of clinical trials is given in Table 1. The World Health Organisation currently recommends that oral zinc supplementation should be given to children with acute or persistent diarrhoea in a dose of 10–20 mg/day.\textsuperscript{32} Further research is needed to establish sustainable ways of supplementing large numbers of apparently well-nourished children in the general population.

**Zinc and Acute Respiratory Infections**

Most studies to assess the association between respiratory morbidity and zinc have been conducted in children who were...
healthy or recovering from an episode of acute diarrhoea at the time of enrolment. Similar to observations in acute diarrhoea, healthy children with low zinc concentrations at the time of enrolment had higher incidences of acute respiratory infections (ARI) during follow-up than children with normal zinc levels.\textsuperscript{22} Initial clinical trials to assess the effect of zinc supplementation on the prevention of ARI showed that zinc reduced the incidence of serious ARI (odds ratio 0.59, 95\% CI 0.41–0.83)\textsuperscript{3} and reduced respiratory morbidity in the 2 months following supplementation of malnourished children.\textsuperscript{38} These studies also found that supplementation had a more general effect on morbidity. For example, in Ecuador, malnourished children supplemented for 60 days had a lower incidence of fever, cough and upper respiratory infections than children not supplemented.\textsuperscript{39} More recent, larger trials in Bangladesh and India have confirmed that there is a lower incidence of ARI in supplemented children.\textsuperscript{4,26,40,41} However, this beneficial effect is not as clear-cut as in diarrhoea\textsuperscript{38,42} and several studies have obtained conflicting results, reporting, for instance, that its effect benefits only boys or those predisposed to zinc deficiency or malnutrition.\textsuperscript{26,43} In addition, there have been no long-term studies to assess its effect on the absorption of other key nutrients such as copper.

Data on zinc supplementation as an adjunct for treating acute pneumonia are scarce. In India, zinc supplementation had no beneficial effect on measles-associated pneumonia\textsuperscript{44} and a recent study to assess the effect of zinc and/or vitamin A supplementation on the clinical outcome of severe acute lower respiratory infection concluded that zinc supplementation is associated with

<table>
<thead>
<tr>
<th>Country</th>
<th>Type of study</th>
<th>Outcome</th>
<th>Supplemented/controls</th>
<th>Age (mths)</th>
<th>Main findings</th>
<th>Ref. no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethiopia</td>
<td>RCT</td>
<td>Growth and morbidity</td>
<td>92/92</td>
<td>6–12</td>
<td>Lower diarrhoea incidence in stunted children</td>
<td>23</td>
</tr>
<tr>
<td>Burkina Faso</td>
<td>RCT</td>
<td>Morbidity</td>
<td>341/344</td>
<td>6–31</td>
<td>Reduced prevalence of diarrhoea</td>
<td>24</td>
</tr>
<tr>
<td>India</td>
<td>RCT</td>
<td>Diarrhoea incidence</td>
<td>1241/1241</td>
<td>6–30</td>
<td>Lower diarrhoea incidence, prevention of prolonged diarrhoea and high stool output</td>
<td>25</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>RCT</td>
<td>Growth and morbidity</td>
<td>152/149</td>
<td>4–24 wks</td>
<td>No effects on diarrhoea morbidity</td>
<td>26</td>
</tr>
<tr>
<td>India</td>
<td>RCT</td>
<td>Malnourished children with diarrhoea</td>
<td>44/36</td>
<td>3–24</td>
<td>Fewer liquid stools and ORS requirements</td>
<td>27</td>
</tr>
<tr>
<td>Nepal</td>
<td>RCT</td>
<td>Acute diarrhoea</td>
<td>447 zinc 450 zinc + vit. A, 452 placebo</td>
<td>6–35</td>
<td>43–47% reduced risk of prolonged diarrhoea</td>
<td>28</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>Cluster RCT</td>
<td>Acute diarrhoea</td>
<td>3974/4096</td>
<td>3–59</td>
<td>Better outcome of diarrhoea</td>
<td>4</td>
</tr>
<tr>
<td>Brazil</td>
<td>RCT</td>
<td>Acute diarrhoea</td>
<td>37/37</td>
<td>&lt;5 y</td>
<td>Reduction of non-injury mortality</td>
<td>29</td>
</tr>
<tr>
<td>India</td>
<td>RCT zinc/ zinc in ORS</td>
<td>Acute diarrhoea</td>
<td>404 zinc syrup 402 zinc-ORS 401 ORS only</td>
<td>6–35</td>
<td>Shorter diarrhoea duration; ORS zinc: reduced number of stools, less effective than zinc alone</td>
<td>31</td>
</tr>
</tbody>
</table>

RCT, randomised controlled trial.
shorter duration of fever and severely ill status, but that this benefit is mostly observed in boys.\textsuperscript{43}

There is therefore evidence that zinc supplementation is effective in preventing ARI as well as diarrhoea and it could be introduced along with vitamin A supplementation. A summary of the studies reported to date is given in Table 2. The beneficial effect of zinc in the treatment of acute pneumonia, however, is still debated and further studies are required to identify the specific groups of children who would benefit most if it were used as an adjunct to current therapies.

### Malaria

Although children with acute malaria often have hypozincaemia, no cohort studies similar to those described for ARI and diarrhoea have examined the association between a preceding deficiency and the development of clinical malaria. Zinc levels in children who have had malaria increase 72 hours after recovery,\textsuperscript{45} suggesting that the low concentrations observed during the acute symptomatic infection are likely to reflect the redistribution from the blood to other organs that occurs during the acute phase response.

**TABLE 2. Studies to assess the effect of zinc on acute respiratory infections.**

<table>
<thead>
<tr>
<th>Country</th>
<th>Type of study</th>
<th>Characteristics on enrolment</th>
<th>No. of participants</th>
<th>Outcome</th>
<th>Age (mths)</th>
<th>Main findings</th>
<th>Ref. no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>Cohort</td>
<td>Recovering from diarrhoea</td>
<td>116</td>
<td>ALRI</td>
<td>12–59</td>
<td>Higher prevalence of LRTI in those with low zinc at enrolment</td>
<td>22</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>RCT</td>
<td>Malnourished, acute diarrhoea</td>
<td>32/35</td>
<td>URTI</td>
<td>3–24</td>
<td>Lower respiratory morbidity 2 months after supplementation</td>
<td>38</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>Cluster RCT</td>
<td>With diarrhoea</td>
<td>3974/4096</td>
<td>LRTI</td>
<td>3–59</td>
<td>Lower incidence of subsequent LRTI</td>
<td>4</td>
</tr>
<tr>
<td>Ecuador</td>
<td>RCT</td>
<td>Malnourished</td>
<td>25/25</td>
<td>URTI and LRTI</td>
<td>12–59</td>
<td>Less fever, cough and upper respiratory tract secretions.</td>
<td>39</td>
</tr>
<tr>
<td>India</td>
<td>RCT</td>
<td>Normal</td>
<td>1241/1241</td>
<td>LRTI, pneumonia, ALRI, growth and morbidity</td>
<td>6–30</td>
<td>Lower incidence of pneumonia</td>
<td>41</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>RCT</td>
<td>Normal</td>
<td>152/149</td>
<td></td>
<td>1–6</td>
<td>Lower risk of LRTI in infants with low baseline zinc</td>
<td>26</td>
</tr>
<tr>
<td>India</td>
<td>RCT</td>
<td>After measles</td>
<td>42/43</td>
<td>Measles-related pneumonia Recovery from LRTI</td>
<td>9 m–15 y</td>
<td>No beneficial effect</td>
<td>44</td>
</tr>
<tr>
<td>India</td>
<td>RCT</td>
<td>Severe LRTI</td>
<td>38 zinc + vit. A, 38 vit. A, 39 zinc, 38 placebo</td>
<td>Recovery from LRTI</td>
<td>2–24</td>
<td>Earlier resolution of fever and very ill status in boys but not girls.</td>
<td>43</td>
</tr>
<tr>
<td>Guatemala</td>
<td>RCT</td>
<td>Normal children</td>
<td>45/44</td>
<td>Diarrhoea and ARI morbidity</td>
<td>6–9</td>
<td>Higher ARI incidence and prevalence in zinc-supplemented group (not statistically significant)</td>
<td>35</td>
</tr>
</tbody>
</table>

ALRI, acute lower respiratory infection; URTI, upper respiratory tract infection; LRTI, lower respiratory tract infection.
A trial in Papua New Guinea reported that zinc supplementation reduced the incidence of *Plasmodium falciparum* episodes and protected children against heavy parasitaemia.\(^46\) A second study in The Gambia also reported that clinic visits attributable to malaria were fewer in the zinc-supplemented group than in the placebo group, although the results did not reach statistical significance.\(^47\) Later studies, however, have not replicated these findings (Table 3). In Burkina Faso, zinc supplementation had no effect on malaria morbidity in children\(^24\) and further studies of acute uncomplicated falciparum malaria in Africa and Ecuador failed to demonstrate any beneficial effect.\(^45\) Most studies on malaria, therefore, do not support the hypothesis that zinc supplementation might play a role in preventing or treating acute malaria.

**Tuberculosis, Lepromatous Leprosy and Leishmaniasis**

Tuberculosis (TB), lepromatous leprosy (LL) and leishmaniasis share the same pathological background. Th1 cytokines are implicated in the mechanisms that mediate host resistance and Th2 cytokines are associated with increased host susceptibility.\(^48\) The pathogens for these diseases are also intracellular\(^49\) and concurrent leprosy and TB infections are not rare,\(^30\) with occasional triple infections with cutaneous leishmaniasis, LL and pulmonary TB (PTB) without concomitant immunodeficiency being reported.\(^51\)

Zinc deficiency might play a yet unexplored role in the immune alterations that modify the predominantly cellular Th1 responses, required for their control, and humoral Th2 responses.\(^52,53\) In human models of zinc deficiency, the production of tumour necrosis factor-\(\alpha\) (TNF-\(\alpha\)), interferon-\(\gamma\) (IFN-\(\gamma\)) and interleukin-2 (IL-2) by peripheral blood mononuclear cells, which are all Th1 products, is decreased, whereas products of Th2 cells (IL-4, -6 and -10) are unaffected. These changes, however, are readily reversed with zinc supplementation.\(^54\) High susceptibility to TB has also been observed in TNF-deficient mice\(^55\) and challenge with *Mycobacterium tuberculosis* in anti-IFN-\(\gamma\) monoclonal antibody-treated mice results in significantly higher bacterial loads in the lungs.\(^56\) Moreover, the administration of IFN-\(\gamma\) to CD4-depleted mice infected with *M. tuberculosis* significantly reduced their bacterial loads.\(^56\) In humans, treatment of certain diseases with anti-TNF-\(\alpha\), e.g. infliximab, led to the activation of latent TB,\(^57–59\) and a mutation in the gene for IFN-\(\gamma\) receptor results in increased susceptibility to mycobacterial infection.\(^60\) All this suggests that zinc

<table>
<thead>
<tr>
<th>Country</th>
<th>Type of study</th>
<th>Outcome</th>
<th>Zinc/controls</th>
<th>Age</th>
<th>Main findings</th>
<th>Ref. no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papua New Guinea</td>
<td>RCT</td>
<td><em>P. falciparum</em> morbidity</td>
<td>136/138</td>
<td>6–60 m</td>
<td>Reduced incidence of <em>P. falciparum</em>, protection against heavy parasitaemia</td>
<td>46</td>
</tr>
<tr>
<td>Gambia</td>
<td>Quasi RCT</td>
<td>Morbidity, growth and biochemical indices</td>
<td>55/55</td>
<td>6–28 m</td>
<td>Fewer clinic visits attributable to malaria (not statistically significant)</td>
<td>47</td>
</tr>
<tr>
<td>Burkina Faso</td>
<td>RCT</td>
<td>Prevention of childhood morbidity</td>
<td>341/344</td>
<td>6–31 m</td>
<td>No effect</td>
<td>24</td>
</tr>
<tr>
<td>Ecuador/Africa</td>
<td>RCT</td>
<td>Uncomplicated malaria</td>
<td>542/545</td>
<td>6–5 y</td>
<td>No effect</td>
<td>45</td>
</tr>
</tbody>
</table>
deficiency might give rise to increased susceptibility to leishmaniasis and TB, although there are have been no epidemiological studies to support this hypothesis.\textsuperscript{61,62} As impaired cellular immunity is also implicated in the pathogenesis of LL, it is possible that zinc-deficient individuals have a higher risk of activation of LL.

**Tuberculosis**

In patients with TB, hypozincaemia is often observed at the time of diagnosis.\textsuperscript{63–71} These low concentrations are strongly associated with the acute response and TB patients with raised C-reactive protein (CRP) have lower serum zinc concentrations than those without raised CRP.\textsuperscript{2} Zinc supplementation increases the tuberculin induration diameter in children exposed to adults with PTB,\textsuperscript{72} and zinc in combination with vitamin A has resulted in earlier clearance of acid-fast bacilli from sputum and resolution of chest X-ray cavities in Indonesian adults with smear-positive PTB.\textsuperscript{73} Similar to the Indonesian study, an earlier but smaller study in India observed that zinc supplementation alone resulted in earlier sputum smear conversion,\textsuperscript{67} and a small study in Ethiopia (unpublished) using weekly zinc supplementation as an adjunct to TB therapy resulted in earlier sputum conversion, although the sample size was only 28 patients. These findings could be related to the increased production of IL-2. IL-2 could be a critical cytokine in the recovery from TB. Studies in Bangladesh and South Africa showed that administration of IL-2 as an adjunct to anti-TB treatment led to decreased sputum bacillary loads\textsuperscript{75} with improved sputum clearance and radiographic resolution.\textsuperscript{76} In a larger trial in Uganda, the administration of IL-2 resulted in earlier sputum culture conversion, 30\% of the 48 patients converting to culture-negative at 1 month compared with 17\% in a placebo group ($n=47$), and at 2 months this ratio was 85\% vs 77\%, respectively.\textsuperscript{77} Moreover, in The Gambia and Guinée, West Africa, untreated HIV-negative patients with pulmonary TB exhibited low Th1 and high Th2 activity \textit{in vivo}, as evidenced by serological markers such as soluble lymphocyte activation gene-3 or soluble CD 30, and better responses to anti-TB treatment were associated with higher Th1/Th2 ratios at the end of the treatment.\textsuperscript{78} Table 4 provides a summary of

<table>
<thead>
<tr>
<th>Country</th>
<th>Type of study</th>
<th>No. in intervention/ control group, type of intervention</th>
<th>Age</th>
<th>Main findings</th>
<th>Ref. no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indonesia</td>
<td>RCT</td>
<td>40/40, zinc + vit. A</td>
<td>Adult</td>
<td>Earlier sputum conversion, resolution of chest X-ray lesions and clinical improvement.</td>
<td>73</td>
</tr>
<tr>
<td>India</td>
<td>RCT</td>
<td>15/24, zinc</td>
<td>Adult</td>
<td>Earlier sputum conversion, not statistically significant at week 4.</td>
<td>67</td>
</tr>
<tr>
<td>Bangladesh &amp; South Africa</td>
<td>Descriptive</td>
<td>8 drug-sensitive TB, 7 MDRTB, rIL-2</td>
<td>Adult</td>
<td>2 MDRTB patients showed clinical and X-ray improvement. Decreased bacillary load in 5 of 6 MDRTB</td>
<td>105</td>
</tr>
<tr>
<td>South Africa</td>
<td>RCT</td>
<td>21/14, IL-2: 12 daily and 9 intermittent</td>
<td>Adult</td>
<td>Faster smear conversion and chest X-ray improvement with daily IL-2.</td>
<td>76</td>
</tr>
<tr>
<td>Uganda</td>
<td>RCT</td>
<td>48/47, IL-2</td>
<td>Adult</td>
<td>Earlier sputum culture conversion (not statistically significant)</td>
<td>77</td>
</tr>
</tbody>
</table>

MDRTB, multi-drug-resistant TB; rIL-2, recombinant IL-2.
these studies. Although it is likely that these effects will be observed in children, to date no studies have investigated the role of zinc in treating children with TB.

Leprosy

A number of studies have reported hypozincæmia in adults with leprosy.\textsuperscript{50,79–84} It is not often observed in adults with tuberculoid leprosy (TT),\textsuperscript{79} but there is a gradual reduction in serum zinc concentrations as severity moves from TT to LL.\textsuperscript{85} It has been reported that zinc concentrations are lower in adults with LL than in those with TT\textsuperscript{84} and the lowest concentrations have been found in patients with erythema nodosum leprosum (ENL) reactions.\textsuperscript{81} Although the significance of these findings is unclear, they might be associated with the fact that the acute phase response is stronger in LL than in TT.\textsuperscript{86}

There have been few clinical trials of zinc supplementation in leprosy. In India, zinc supplementation resulted in better control of chronic ENL reactions\textsuperscript{87} and better clinical outcome along with a tendency to upgrade in patients with multibacillary leprosy.\textsuperscript{80} The cell-mediated immunity (CMI) response is markedly suppressed in LL and upgrading reactions are known to be caused by an increase in CMI, in particular a predominance of Th1 cytokines.\textsuperscript{88} These effects might also be mediated by increased production of IL-2, as giving IL-2 to lepromatous leprosy patients had a significant effect in decreasing the burden of Mycobacterium leprae.\textsuperscript{89,90}

Leishmaniasis

Studies on zinc and its relation to leishmaniasis in humans are scarce. Mice fed with zinc and iron-deficient diets manifested earlier leishmania visceralisation than zinc- and iron-replete controls.\textsuperscript{91} In humans, the low serum zinc concentrations in patients with cutaneous leishmaniasis increase during antimonial therapy.\textsuperscript{92} This might be owing to pre-existing zinc deficiencies or related to the redistribution associated with the acute phase response of visceral leishmaniasis (VL).\textsuperscript{93,94} As an analogy to the findings described for TB, local administration of IL-2 results in enhanced cellular immunity with a reduction of parasite load in cutaneous lesions of patients with disseminated cutaneous leishmaniasis,\textsuperscript{95} and administration of IFN-\gamma as an adjunct to pentavalent antimony therapy for VL resulted in a better clinical outcome (Table 5).\textsuperscript{96,97}

Zinc Toxicity

Zinc supplementation at physiological doses is considered to be safe, although there are potential side-effects that need to be considered. Moderate doses of zinc supplements can give a metallic flavour and induce nausea and vomiting.\textsuperscript{98} These symptoms, however, have not been reported as significant side-effects in clinical trials that used short-term supplementation for the prevention or treatment of acute diarrhoea or respiratory infections. Large oral doses of zinc can interfere with copper bio-availability as they compete for absorption,\textsuperscript{99} and clinical signs of immune dysfunction have been reported with daily doses in excess of 150 mg.\textsuperscript{99,100} In addition, a small, randomised clinical trial of 141 severely malnourished children in Bangladesh\textsuperscript{101} reported that children receiving 6 mg/kg of zinc for 15 days had a higher mortality than children receiving lower doses. In addition, in poorly ventilated mining industries and during galvanization of iron, welding and manufacture of brass, zinc in the air can reach toxic levels, posing a significant health risk to workers chronically exposed.\textsuperscript{102} Finally, a recent large study in the USA reported that men who consumed >100 mg/day had an increased risk of advanced prostate cancer.\textsuperscript{103} These findings were observed only in patients receiving high-dose supplements and
chronic zinc deficiency has also been associated with an increased risk of prostate cancer. Elderly patients in the United States are currently recommended to consume moderate amounts of zinc as a preventive measure against age-related macular degeneration and prostate cancer. It is therefore prudent to recommend that further studies should use zinc supplementation at low to moderate doses and within physiological ranges.

**Conclusion**

There is substantial evidence that zinc supplementation is beneficial for the prevention and treatment of acute and persistent diarrhoea and supplementation of children during acute and persistent episodes is recommended. Its effect in the prevention of respiratory infections is less striking. Supplementation of children seems to reduce the incidence of ARI, although some studies suggest that this benefit occurs only in certain high-risk groups. Only one study demonstrates that supplementing children who have ALRI improves their recovery. The diagnostic criteria for respiratory infections have varied between studies and further investigations should be conducted to elucidate its potential role in the treatment of ALRI. Zinc supplementation is not effective for the prevention of malaria; larger trials have not replicated results of initial reports that suggested a beneficial effect. Preliminary studies on TB suggest a possible role of zinc in improving clinical outcome in adults. This effect might be mediated by the increased production of selected cytokines and enhancement of the Th1 response, although there are other possible mechanisms. If initial reports in adults are confirmed by larger studies, zinc

<table>
<thead>
<tr>
<th>Country</th>
<th>Type of study</th>
<th>No. in intervention/control group, type of intervention</th>
<th>Age</th>
<th>Main findings</th>
<th>Ref. no</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>Descriptive</td>
<td>40 with leprosy, zinc</td>
<td>Adult</td>
<td>Better control of chronic ENL reactions</td>
<td>87</td>
</tr>
<tr>
<td>India</td>
<td>Comparative non-randomised trial</td>
<td>15/10 multi-bacillary leprosy, zinc</td>
<td>Adult</td>
<td>Better clinical outcome, re-growth of eyebrows, reduction in bacterial index, Tendency to upgrade.</td>
<td>80</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>Descriptive</td>
<td>35 leprosy patients, IL-2 injection</td>
<td>Adult</td>
<td>Reduction of bacillary load and enhanced cellular immunity</td>
<td>90</td>
</tr>
<tr>
<td>Nepal</td>
<td>Descriptive</td>
<td>14 leprosy patients, IL-2 injection</td>
<td>12–56 y</td>
<td>Decreased bacillary load</td>
<td>89</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>Descriptive</td>
<td>3 patients, disseminated cutaneous leishmaniasis, IL-2 injection</td>
<td>Adult</td>
<td>Clearance of amastigotes by enhancing cellular immunity</td>
<td>95</td>
</tr>
<tr>
<td>Brazil</td>
<td>Non-randomised trial</td>
<td>17 VL patients, IFN-γ injection</td>
<td>2–23 y</td>
<td>Improved clinical outcome, reduction of leishmania index of splenic aspirates</td>
<td>97</td>
</tr>
<tr>
<td>Kenya</td>
<td>RCT</td>
<td>10/14, IFN-γ injection</td>
<td>5–32 y</td>
<td>Faster negative splenic aspirate</td>
<td>96</td>
</tr>
</tbody>
</table>

**TABLE 5. Studies on zinc, IL-2 and IFN-γ and leprosy or leishmaniasis.**

ENL, erythema nodosum leprosum.
supplementation might improve the success rate of anti-TB treatment in children. There is a need to initiate studies to investigate its potential role in children with TB. Data on the relationship between zinc, leishmaniasis and lepromatous leprosy are scanty; however, available information suggests that zinc might play a role in preventing LL and treatment of both conditions and further studies should be encouraged.

References


81 George J, Bhatia VN, Balakrishnan S, Ramu G. Serum zinc/copper ratio in subtypes of leprosy and...


