

COMMENTARY

Zinc supplementation for infants

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The potential impact of zinc deficiency on infant, child, and maternal health in developing countries was not recognised by the United Nations until 1997, when zinc was included among the micronutrient deficiencies listed as a priority in the Third Report on the World Nutrition Situation.¹ The true magnitude of mild and moderate zinc deficiency in developing countries is unknown, in part because of the lack of a reliable index of zinc status.² The best method of confirming zinc deficiency is to show a physiological response to zinc supplementation in a double-blind placebo-controlled trial. Such a trial is reported in today's *Lancet* by Melaku Umeta and colleagues, who investigated the effect of a zinc supplement on growth, body composition, appetite, and morbidity in stunted and non-stunted rural Ethiopian infants aged 6–12 months. Unlike several earlier zinc-supplementation studies of infants in developing countries,^{3,4} these Ethiopian infants were not severely malnourished, but apparently healthy and free from intestinal parasites. Whether they were of normal birthweight and gestational age is not known.

The infants were matched by sex, age, and length before random assignment to a placebo or zinc supplement administered as a syrup 6 days a week for 6 months. The zinc supplement (as zinc sulphate) was given after breastfeeding but before any complementary foods, thus minimising the possibility that inhibitors in these foods might compromise the bioavailability of zinc in the supplement.⁵ The significantly higher serum and hair zinc concentrations in the supplemented than in the placebo groups at the end of the trial confirmed both compliance with the supplement and its absorption. The dose of the zinc supplement (10 mg Zn) was higher than that given in most earlier zinc-supplementation trials in apparently healthy infants in developed countries.^{4,6} Because such a high dose of zinc can potentially induce antagonistic interactions with iron and copper, sensitive biochemical indices of iron (eg, transferrin receptor) and copper (eg, erythrocyte copper and zinc superoxide dismutase) status, preferably before and after intervention, would have provided reassurance that iron and copper status were not adversely affected.

Umeta and colleagues showed significant effects of the zinc supplement on linear and ponderal growth in both the stunted and non-stunted infants; the two effects were much greater for the stunted infants, a trend consistent with findings of a meta-analysis of 22 double-blind zinc-supplementation studies in children.⁶ The difficulties that the investigators encountered during the measurement of

knee-heel length may explain why this variable did not seem to respond to the zinc supplement. The growth responses were apparently independent of sex, although in earlier studies boys benefited more than girls from zinc supplementation,⁴ perhaps because boys have higher estimated zinc requirements than do girls during infancy.⁷ Although abnormalities in skeletal growth and mineralisation may occur in zinc deficiency,⁸ they were not investigated in this Ethiopian study.

Unlike studies in the Gambia,⁹ Uganda,¹⁰ and Guatemala,¹¹ no significant changes in mid-arm circumference or triceps skinfolds were reported in Umeta and colleagues' study, even though the supplemented stunted Ethiopian infants showed an improvement in appetite as perceived by the caregiver. Zinc might induce the changes in body composition by one or more of the following means—an increase in lean-tissue accretion, an improvement in appetite and thus energy intake, or an improvement in the efficiency of use of dietary energy and protein. Certainly, muscle growth is affected in zinc deficiency. Animal studies have indicated that, in zinc deficiency, the synthesis of muscle tissue is more limited than that of fat because of defective protein synthesis, although there is no change in the zinc concentration in the muscle. Malnourished Jamaican children with chronic marginal zinc deficiency and undergoing nutrition rehabilitation showed greater gains in fat than muscle, until supplemented with zinc, when proportionately more lean-tissue accretion occurred.¹²

What mechanisms underlay the zinc-responsive growth retardation observed in the Ethiopian infants is not well established. Probably critical, but not emphasised by Umeta and colleagues, is the direct role of zinc in protein synthesis and gene expression, and in hormonal imbalances. In the Ethiopian study, the positive growth response was attributed, in part, to a secondary impact of zinc on growth resulting from reductions in the incidence of anorexia and morbidity from cough, diarrhoea, fever, and vomiting in the stunted children. Substantial reductions in rates of diarrhoea (25% for prevalence and 18% for incidence) and pneumonia (41% for incidence) in children in developing countries supplemented with zinc have been confirmed in a pooled analysis of ten randomised controlled trials,¹³ and attributed to the role of zinc in both cellular and humoral immune functions. Indeed, the effect of zinc supplementation on prevention of diarrhoea is said to be as much as the WHO estimated reduction in childhood diarrhoea (27%) achieved by high-quality improvements in water and sanitation.

Hair and serum zinc concentrations measured in half

the infants in each study group after intervention suggest that the stunted Ethiopian infants had a lower initial zinc status than did their non-stunted counterparts. In addition, at the end of the study concentrations of zinc in serum and hair correlated positively with linear growth in the zinc-supplemented stunted infants, which emphasises the major association between zinc deficiency and stunting. The study also highlights the use of hair zinc as a valid and non-invasive index of chronic zinc status during infancy.

The cause of the growth-limiting zinc-deficiency syndrome in these breastfed Ethiopian infants was not extensively investigated. A low zinc content of breastmilk was unlikely to be a factor because zinc in breastmilk is generally not affected by maternal diet. More critical factors might be the high zinc requirements for growth, coupled with inadequacies in the content or bioavailability of zinc in the cereal-based complementary foods.⁵ Excessive endogenous zinc losses from diarrhoea would also be an exacerbating factor.

Umeta and colleagues' study breaks new ground in showing that zinc is the primary growth-limiting nutrient during infancy in African children. An earlier Gambian study did not show any impact of a zinc supplement on linear or ponderal growth during infancy, or any biochemical evidence of zinc deficiency.⁹ These discordant findings highlight the probability that zinc is only one of the dietary factors that may cause stunting. Indeed, in many developing countries, deficiencies in other nutrients may limit a growth response to zinc supplementation. Whether zinc is the primary growth-limiting nutrient during infancy will depend on the ecological setting. Influencing factors include breastfeeding practices, the amount and dietary quality of the complementary foods offered, the frequency, duration, severity, and type of infections, especially diarrhoeal episodes, and the potential constraints on growth induced by long-term effects of prenatal malnutrition and inter-generational effects of maternal malnutrition. Universal zinc supplementation will not improve the growth of stunted children unless zinc is the primary growth-limiting nutrient. Caution must be observed when selecting the dose of zinc supplements, especially for catch-up growth in children with severe protein-energy malnutrition and an already compromised immune system. In such circumstances, high doses of zinc supplements may increase morbidity³ and mortality.¹⁴

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Prevention of paracetamol poisoning

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Paracetamol poisoning, intentional and unintentional, has been a public health issue since the 1970s. An epidemic of paracetamol-related suicide in the UK in the 1980s and the subsequent unrelenting upward trend in paracetamol morbidity and mortality noted there and elsewhere during the 1990s represent a clear imperative for population-based measures to alleviate this potentially preventable burden of suffering.

This issue of *The Lancet* presents two Research Letters providing some evidence about the outcome of such a measure implemented in the UK in September, 1998, when the amount of paracetamol available at a single purchase without prescription was curtailed from a previously unlimited quantity to a maximum of 100 tablets. In addition, the packaging was changed from a loose-preparation pack, to a blister-pack. J L Turvill and K Moore report that the number of paracetamol overdoses presenting to an accident and emergency department of a London hospital in the 12 months after the change in regulation was implemented was lower than that in the previous 36 months. Martin Prince and colleagues report on a similar trend in the numbers of referrals to a tertiary liver unit and for liver transplantation because of paracetamol-induced hepatic failure.

Both studies show decreases that are clinically as well as statistically significant. However, neither study design can provide definitive evidence of causation. The findings are correlational, not experimental. Other events or factors occurring in September, 1998, or later could have influenced paracetamol poisoning or the means of parasuicide. Furthermore, the sampling strategies (for poisonings of sufficient concern for patients to be seen in an accident and emergency departments or to require hospital admission) might have led to an underestimate of the total number of cases or a bias in the types of cases. Most importantly, neither study differentiated between unintentional and intentional poisoning, nor did they report on paracetamol mortality and completed suicide.

The effectiveness of broad population-based measures can be difficult to determine conclusively. Demonstrating the effectiveness of public policy is contingent upon a sound plan for its evaluation and upon implementation of the policy in a manner allowing a scientifically rigorous evaluation. It is unclear whether the effectiveness of the