Micronutrients in the Treatment of Stunting and Moderate Malnutrition

Mary Edith Penny

Instituto de Investigación Nutricional, Lima, Perú

Abstract
Linear growth retardation or stunting may occur with or without low weight-for-age, but in both cases stunted or moderately malnourished children are deficient in micronutrients. Pregnancy and the first 2 years are critical periods. Dietary deficiency of zinc, iron, calcium, and vitamin A are especially common and often occur together. Zinc is essential for adequate growth, and supplements have been shown to increase intrauterine femur length and to prevent stunting. However, in general, supplements which provide a mixture of micronutrients have been more successful in preventing stunting and are simpler to take and distribute. Multiple micronutrients together with energy and macronutrients are also needed for the management of moderate malnutrition. Multiple micronutrients may be delivered as medicinal-like supplements, but may also be combined with food, for instance in milk drinks, in fortified dried cereal mixes used to supplement complementary foods or in lipid nutrition supplements. The latter also provide essential fats necessary for growth. Micronutrient powders for home fortification are effective in preventing anemia, but present combinations do not prevent stunting. Improving the diets of infant and young children is also possible, and increased intake of animal source foods can improve growth.

Introduction
Infant and child nutritional status is expressed as a weight-for-age, height-for-age, and weight-for-height z scores in relation to the median (50th centile) of a reference population. Linear growth retardation leads to stunting, which is defined as length or height-for-age z score less than −2. Stunting is a chronic process that represents a personal history of deprivation and has lifetime consequences [1]. Low weight-for-age can be a consequence of acute malnutrition associated with loss of fat and lean body mass resulting in thinness (low weight-
for-height) or result from chronic low growth rate when it is often associated with stunting and intrauterine growth retardation. Moderate malnutrition (MM) is defined variously as weight-for-age z scores between –2 and –3 SD [2] or weight-for-length-/height-for-age (wasting) between –2 and –3 SD [2]. Children with MM are at risk of long-term adverse consequences [3].

The new WHO growth reference standards have provided a benchmark against which population and individual child growth and nutritional status can be compared [4], and the strikingly similar growth pattern of children from different ethnic and geographical conditions adds to existing evidence that in the first 5 years it is possible to use a single reference to compare growth across the world.

While normal growth seems similar across populations, the pattern of growth of children in different low resource situations is not. Figure 1 is an example of the considerable difference in early growth between babies born in South Asia compared with babies in South and Central America. In the latter area, the most common growth deficit is stunting in the absence of low weight, whereas in South Asia low birthweight is common, and more than 40% of young children are underweight. Treatment and prevention guidelines need to take this into consideration, and I will consider the role of individual micronutrients in the prevention and treatment of stunting and MM separately.

**Stunting**

Linear growth retardation often begins in utero, but is most marked during the vulnerable period of complementary feeding, the transition from a diet of breast milk to the family food [5]. While dietary intakes of breast milk plus

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**Fig. 1.** Patterns of growth of 0- to 6-month-old children in South Asia and Latin and Central America from selected national demographic and health surveys.
complementary foods usually meet protein requirements, energy intakes may be low, and diets are almost always low in critical micronutrients, especially calcium, iron and zinc, both in absolute terms and in terms of nutrient density. Vitamin A is also deficient in some areas, and dietary deficiency of niacin, riboflavin, thiamine, B₆, B₁₂, vitamin C, vitamin D, magnesium, phosphorus and potassium have been reported [6–9]. These micronutrients, except vitamin C, are typically associated with animal source foods (ASFs). ASFs are especially good sources of minerals such as iron, zinc and calcium because of relatively high concentrations and bioavailability. Inhibitors, such as phytates and fiber, present in cereals and legumes, reduce the dietary utility of minerals from plant sources. Diets that are high in cereal content and low in ASFs have been associated with stunting [10, 11].

**Zinc**

Zinc is essential for many physiological processes, and severe zinc deficiency leads to dwarfism [12]. Zinc deficiency is common in many populations [13]. Two out of three recent meta-analyses [14–16] of clinical trials of zinc supplementation in children report a large and significant effect of daily oral zinc supplements on linear growth especially in stunted children and in developing countries. Imdad and Bhutta [16] reported the greatest impact when zinc was given alone, and estimated that in children under 5 years there was a net gain of 0.37 ± 0.25 cm for a dose of 10 mg zinc daily for 24 weeks.

Antenatal zinc supplementation has been shown to increase fetal long bone growth [17], of particular relevance because nutritional stunting is due to short femur length [18]. A study in Nepal showed a small but significantly greater height in school children whose mothers received antenatal zinc supplements [19], but a large study of antenatal zinc supplements reported no effect on postnatal growth, although the offspring of supplemented mothers had reduced prevalence of diarrhea and other infections [20]. Zinc supplements have been repeatedly shown to prevent respiratory complications and diarrhea in infancy, themselves associated with stunting. The benefit of zinc may be limited by the continuing infection or by the presence of other nutrient deficiencies. A study combining zinc and antiparasite treatment reported a positive effect of zinc on linear growth that was reduced by the presence of *Giardia lamblia* and *Ascaris lumbricoides* [21].

**Other Single Micronutrients**

No other micronutrient has been so well studied in relation to linear growth as zinc, but large scale trials assessing the importance of other single micronutrients such as vitamin A and iron have often measured growth.
Clinical vitamin A deficiency is associated with poor growth, but although a few studies report increased height gain when children with severe deficiency of vitamin A were given supplements [22], most studies have not reported any significant effect on linear growth or weight gain [15].

Iron deficiency is common, and the hematological and cognitive effects are sufficient reason for supplementation. The impact of iron supplementation on linear growth has been inconsistent. A systematic review by Ramakrishnan et al. [23] reported a nonsignificant tendency towards a positive effect in children who were stunted at baseline, and a review by Sachdev et al. [24] reported significant effects only in some subpopulations: children older than 5 years, in malaria hyperendemic areas and those who received the supplement for longer than 6 months. An update of recent evidence [25] concluded that growth was neither positively nor negatively affected by iron supplementation.

Calcium is essential for bone formation and often deficient in diets low in ASFs, especially when dairy products are absent. Trials of calcium supplementation as a single nutrient have tended to focus on school-aged children rather than infancy when linear growth faltering is maximal. A review of randomized trials concluded that calcium supplements had no impact on growth [26].

Many other micronutrients have a role in normal growth and potentially may contribute to stunting. Severe iodine deficiency for instance causes cretinism, a form of dwarfism, but since important deficits in cognitive development occur even in moderate deficiency, this has been the primary outcome of intervention trials, and linear growth has not been measured.

Other vitamins commonly deficient in cereal-based diets include vitamin B₁₂, folic acid, thiamine, niacin and vitamin D, and because of probable dietary deficiencies these are often included in multi-micronutrient supplements, but their role in preventing stunting has not been established.

Multiple Micronutrients

Given that micronutrient deficiencies rarely occur in isolation, attention has turned to multimicronutrient supplements as an alternative approach. This brings challenges because of interactions, product stability and acceptability, but this approach is very attractive to programs since the logistics and cost of attempting multiple separate daily supplements is prohibitive.

Multiple micronutrients (MMNs) have been assessed in clinical trials in different parts of the world. A review in 2003 [27] of community-based micronutrient supplementation trials concluded that supplements that contained zinc, vitamin A and iron could have positive effects in deficient populations. A meta-analysis in 2004 [23] also reported overall positive effects of MMN supplements on growth in contrast to single nutrient supplements. A recent review by Allen et al. [28] was able to include a further 13 studies. The analysis included studies
that had compared MMNs against single nutrients, mainly iron. This analysis concluded that overall length and height were improved with an effect size of about 0.13 (95% CI: 0.055–0.21). Some studies reported positive effects only in subgroup analyses; for instance, in Mexico a multinutrient beverage was only effective in children under 12 months [29], and in Vietnam [30] the subgroup of children who were stunted at the start of the study showed the largest effect size. MMNs were delivered in a variety of ways, but the analysis was unable to detect whether any particular delivery mode was better than another.

In conclusion, MMN supplements given to infants and young children seem to have a fairly small but positive effect on length or height, and two recent analyses suggest that this is greater than the effect of single micronutrients.

Given that birthweight is associated with postnatal infant growth, micronutrients given antenatally would be expected to reduce infant malnutrition at least during the first few months. A Cochrane review [31] reported that prenatal MMNs were no more effective than iron and folic acid alone in reducing low birthweight and small for gestational age. However, a recent cluster-randomized trial of the INIMMAP MMN prenatal supplement in Niger significantly reduced low birthweight and increased average birthweight but only by 67 g [32]. An effectiveness trial in Vietnam [33] showed an impact on birthweight and also on the height of 2-year-old children including 10% less stunting in the communities where the prenatal supplements had been used. A more recent combined analysis of original data from 12 randomized trials concluded that compared with iron-folic acid, MMNs resulted in a small increase in birthweight and a reduction of low birthweight by about 10% [34]. Information about the infant’s postnatal growth was not included.

Thus, it seems that MMNs are an effective intervention to prevent or treat stunting in infants and young children, but more needs to be studied about means of delivery and the potential impact of prenatal supplementation, particularly in preventing the growth retardation in the first 6 months that has been revealed by the WHO growth reference [35].

**Moderate Malnutrition**

Moderate malnutrition may arise either because a previously ‘normal’ child has lost weight or failed to gain weight and crosses ‘growth centiles’ or because a low birthweight baby continues to track along a low ‘centile’ corresponding to less than 2 SD below the norm. These two scenarios are very different in clinical terms, but cannot be distinguished by a single measurement, and for this reason in evaluating individuals longitudinal growth data whenever available should always be examined. Thus, moderate malnutrition, in contrast to stunting does not necessarily represent a chronic dietary inadequacy; however, recovery from moderate malnutrition will always require an increase in body mass implying
increased energy and protein needs. On the other hand, the treatment of stunting with additional calories, especially in the context of Latin America where stunting is often associated with above average weight-for-height, may potentially lead to increased overweight or obesity, and should be carefully controlled.

A recent World Health Organization call for action and consultation on the management of moderate malnutrition in children under 5 years of age has addressed the issues related to managing moderate malnutrition and provides an excellent review of all the issues involved in rising to the challenge of treating these children [2]. The nutrient needs of children have been considered and a number of nutrients including protein, potassium, phosphorus as well as energy, essential fatty acid and MMNs are considered important. In terms of micronutrients, there is emphasis on the need to ensure sufficient intake of all type 2 micronutrients, those associated with growth. Although single micronutrients such as iron [24, 25], vitamin A [22] and zinc have been associated with weight gain, since children with moderate malnutrition are especially likely to have multiple nutrient deficiencies, the role of single micronutrients may be less significant, and MMNs have usually been considered; in fact, the expert consultation went as far to say that ‘approaches putting emphasis on single nutrients are misguided and should be abandoned’ [2].

There is considerable debate over the amounts of micronutrients that should be included in multi-micronutrient mixes whether in food or as supplements, and the expert consultation suggested that the requirements be set between the daily recommended intakes for eutrophic children and the contents of the F100 diet designed for management of severe malnutrition with the latter providing a safe upper limit. The same consultation provided detailed background and thoughtful recommendations not only on the content of foods but also relevant foods and ingredients including anti-nutrients, and the reader is referred to this report for further information [2]. In addition, attention is given to the important complementary activity of dietary counseling [2].

**Delivery of Multiple Micronutrients**

The evidence so far suggests that both for the treatment and prevention of stunting and for moderate malnutrition MMNs are indicated. So what options are available for delivery of these micronutrients, and what are the issues involved?

Many different formulations have been tried in clinical trials of micronutrients, but there are some emerging leaders in the field. For more than 30 years, food assistance programs have distributed food aid for the prevention and treatment of malnutrition and for emergencies as fortified food blends [2]. These are intended to replace or add to local traditional complementary foods. These mixtures usually contain blends of cereals such as corn, soy beans, sugar and oil and are distributed by international agencies. In many countries there are
also local products such as Incaparina of Guatemala, and Mi Papilla in Ecuador. These products can be successful in reducing anemia, but have had less impact on stunting or moderate malnutrition. Ecuador children attending participating health facilities who were offered counseling and ‘mi papilla’ had highly significant reductions in anemia compared with those attending control facilities who only received counseling, but differences in height were not significant when confounding variables were controlled [36]. Studies in India, Mexico and Perú have shown less encouraging results with no effect on linear growth faltering, and a review of the PL480 title II foods program included in the moderate malnutrition consultancy [2] illustrated some of the problems of low acceptance and intrafamily sharing of the product that reduced the nutritional benefit to the target child.

Two other categories of fortified foods: complementary food supplements and micronutrient powders are extensively reviewed by the Ten Year Strategy to Reduce Vitamin and Mineral Deficiencies, Maternal, Infant and Young Child Nutrition Working Group: formulation subgroup of the moderate malnutrition consultancy [2]. Complementary food supplements are food based and contain macronutrients and micronutrients designed to complement, rather than replace, other foods prepared in the family. Micronutrient powders are mixtures of vitamins and minerals that are added to traditional foods. They do not include macronutrients in significant dietary amounts.

### Complementary Food Supplements

These supplements include the highly nutrient-dense spreads described by Briend [37] also known as ready to use therapeutic food, and now being successfully used for the treatment of severe and moderate malnutrition [2]. These lipid nutrient supplements (LNS) are based on high-fat products such as peanut butter or soy beans with added micronutrients with or without milk. They have the benefit of being highly palatable with good acceptability. They provide an excellent medium for micronutrients, and essential fatty acids can be added, and because of the low water content, bacterial growth is inhibited. A study in Malawi confirmed better weight gain in moderately malnourished children compared with a cereal product [38], but there was no difference in linear growth. These products are now being developed for use as a food complement in smaller doses and with micronutrients adjusted for treatment of stunting and moderate malnutrition. In addition, a trial of multi-micronutrients delivered as micronutrient powders, LNS and crushable tablets in Ghana showed that while all three supplements reduced anemia and resulted in improved motor function, only the LNS improved linear growth [39]. Cost is a concern with LNS, but it is hoped that local production will address this problem.
Micronutrient Powders

Micronutrient powders presented in small single-use sachets to add to a serving of complementary food have proved successful in preventing and treating anemia [40, 41]. The potential for adding other micronutrients such as zinc has been explored, but as yet no formula has been shown to prevent stunting or promote linear growth.

Improving the Infant and Young Child’s Diet

Another alternative to improve stunting and moderate malnutrition is to improve the child’s normal diet by increasing the micronutrient content and availability. Two approaches have been tried: reducing inhibitors to absorption to enhance bioavailability and increasing consumption of ASFs.

Complementary foods can be processed, for instance by fermentation to reduce phytate content. In Tanzania, processed complementary food reduced phytate but did not improve growth compared with usual household preparations [42]. Another attempt to use maize that had been selected for low phytate content to improve growth was not successful in infants in rural Guatemala [43]. The reduction of inhibitors to mineral absorption may be seen as a complementary strategy to improve complementary foods, but has not yet been shown to enhance growth.

Enhanced nutrition education through the health services in a population where low-cost ASFs are available, resulted in higher intakes of ASFs associated with prevention of stunting [44]. Intake of ASFs was associated with better height gain in Kenyan school children, and weight gain and increased lean body mass was associated with increased meat intake, but only milk intake resulted in height gain [45].

Milk deserves special mention because of its potential role as a vehicle for fortification. Fortified milk given to Indian children resulted in increased linear growth [46] compared with unfortified milk. Milk is of particular interest because it stimulates IGF-I secretion which stimulates growth. Further research is needed to explore milk, fortified or not in programmatic conditions.

Discussion and Future Directions

The evidence suggests that MMNs can reverse to some extent the impact of linear growth retardation in infants and young children whose dietary intake is insufficient. MMN combinations may be more effective than single nutrients and have logistic advantages. New strategies are encouraging, and many programs and countries are now considering how best to implement MMN
supplementation at scale. The combination of micronutrients makes it possible to tailor interventions to the particular needs of different populations addressing the multiple effects of inadequate dietary intakes. We need to take a holistic approach that also includes the health hazards of both deficiency and excess, especially where increasing rates of childhood obesity coexist with stunting and anemia.

References

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