Original Article

Micronutrient supplementation and its relationship to nutritional status, health and diseases

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Micronutrient deficiency is still a major problem in many developing countries and multiple micronutrient deficiencies often occur concomitantly. Micronutrient supplementation may be the preferred option because it is cost-effective. Supplementation with iodized peanut oil was more efficacious and gave a longer protection period in preventing iodine deficiency than did iodized poppy seed oil. Inclusion of vitamin A in the iron supplement improved the vitamin A status of pregnant women and their infants. Daily or weekly multimicronutrient supplementation improved growth of stunted young children, whereas weekly multimicronutrient or iron–folic acid supplementation improved the productivity of female workers. In addition, vitamin A and zinc supplementation improved the impact of tuberculosis medication, particularly during the first 2 months. In conclusion, multimicronutrient supplementation has beneficial effects on the improvement of nutritional status, work productivity, health and diseases. The challenge is how to translate the efficacy of supplementation strategies into a large-scale setting.

Key words: iodine, iron, multimicronutrient, vitamin A, zinc.

Introduction

Micronutrient deficiency is still a major problem in many developing countries. It is estimated that iron deficiency anaemia affects approximately 1.3 billion people,[1] clinical vitamin A deficiencies affect approximately 2.8 million children and subclinical vitamin A deficiency affects approximately 250 million children.[2] In addition, more than 2 billion people are at risk of iodine deficiency disorders (IDD). Besides deficiencies of iron, vitamin A and iodine, other micronutrient deficiencies such as that of zinc, selenium, folate and riboflavin might also afflict a high number of people. Micronutrient deficiencies may reduce resistance to infection, thereby causing frequent and severe infections. Moreover, infections, even when they are mild or subclinical, may worsen nutritional status by a variety of mechanisms.[3]

The risks of micronutrient deficiency change with age.[2] Causes and consequences of early micronutrient deficiencies have implications for later life and may be present as risk factors for future generations. Generally, micronutrient deficiency is a result of negative nutrient balance due to rapid growth of body tissue and/or nutrient losses combined with insufficient nutrient intake. Other factors related to micronutrient deficiency are repeated infections and poor bioavailability of nutrients from food due to the presence of inhibitors or lack of enhancers in foods. Multiple micronutrient deficiencies often occur concomitantly because they share the same aetiology. In addition, a deficiency of one micronutrient is often associated with deficiencies of others, for example, the deficiency of iron may be a result of vitamin A deficiency.[4]

Strategies to minimize micronutrient deficiency include supplementation, fortification and promotion of dietary changes; each of these have strengths and limitations.[5] When fortification and promotion of dietary changes are not feasible in the vulnerable population group and the micronutrient deficiency problem needs to be addressed promptly, supplementation may be the preferred option because it is cost-effective.[6]

Supplementation with iron–folic acid tablets is the most common strategy to combat iron deficiency and iron deficiency anaemia. However, the effectiveness of iron supplementation programmes through primary health care is often low.[7,8] Weekly iron supplementation has been proposed as a method of choice for providing iron supplements given the similar efficacy of daily and weekly iron supplementation in preschool children,[9,10] non-pregnant women[11,12] and pregnant women.[13] Weekly supplementation has been challenged in its application not only as regards iron but also for multimicronutrients.[6]

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One of the research lines at South-east Asian Ministries of Education Organization, Tropical Medicine (SEAMEO TROPMED) Regional Centre for Community Nutrition is on micronutrients, particularly iron, vitamin A, iodine, and zinc. It focuses on the investigation of the magnitude and causes of micronutrient deficiencies and of possible intervention measures. The purpose of the current paper is to present studies on micronutrient supplementation and its relationship to health and diseases in different population groups, which were carried out at SEAMEO TROPMED Regional Centre for Community Nutrition, Jakarta.

Salt intake and iodized oil supplementation

Iodine deficiency is the world's leading cause of preventable mental retardation. The main cause of IDD is inadequate intake of iodine due to environmental deficiency of this essential element. Poverty, remoteness, poor sanitation and general undernutrition may worsen the effects of iodine deficiency. Two main strategies for the effective control of iodine deficiency are provision of iodized salt and injection or oral preparation of iodized oil.

A study of salt consumption of boys (age 8–10 years) and their mothers in East Java revealed that salt consumption for boys was 5.4 ± 2.1 g/day and for mothers 5.8 ± 1.7 g/day, whereas consumption of discretionary salt (lithium-labelled salt given to mothers for 7 days as a replacement of their daily salt) was 50% of the total salt consumed.[14] Discretionary salt intake was assessed for 7 days using lithium-labelled salt as a marker. Total salt intake assessed using the 24-h recall method was 7.01 ± 2.43 g/capita per day, whereas that assessed using the salt weighing method was 5.99 ± 1.88 g/capita per day. This study showed that the intake of salt for boys was not different from that of their mothers. If the salt consumed is iodized at a level of 30 p.p.m. iodine, the population will meet their iodine requirements (iodine intake is approximately 162–174 μg/day).

Provision of iodized salt is sometimes ineffective because of economic conditions, inadequately iodized salt, loss of iodine from salt and a shortage of iodized salt supply.[15] Oral administration of iodized oil has been advocated as an alternative to injection of iodized oil. The available preparation of iodized oil is based on poppy seed oil, which is expensive. Indonesia (PT Kimia Farma) has produced iodized oil based on peanut oil. School-age children (8–10 years; *n* = 251) from an endemic iodine-deficient area were randomly allocated to five groups to receive a single oral dose of placebo, iodized peanut oil (200, 400, or 800 mg I) or iodized poppy seed oil (400 mg I).[16] The efficacy of the iodized poppy seed oil preparation in supplying 400 mg iodine, as indicated by urinary iodine excretion concentration, was similar to iodized peanut oil supplying 200 mg iodine and significantly lower than iodized peanut oil supplying 400 or 800 mg iodine in a 4–50-week follow-up period (Fig. 1). In addition, iodized peanut oil gave a period of protection against iodine deficiency that was twice as long as that provided by iodized poppy seed oil (77 weeks vs 42 weeks, respectively).

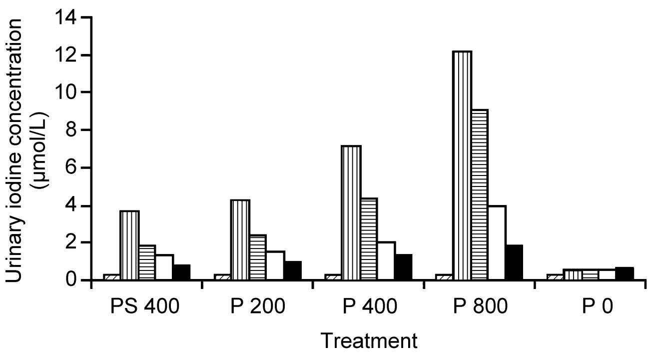

Figure 1. Median urinary iodine concentration before and after five treatments of supplementation. PS 400, poppy seed oil, 400 mg iodine; P 200, peanut oil, 200 mg iodine; P 400, peanut oil, 400 mg iodine; P 800, peanut oil, 800 mg iodine; P 0, peanut oil. All values are different from the baseline in all five treatments, except in P 0.[16] (▨), 0 weeks; (▥), 4 weeks; (▤), 12 weeks; (□), 25 weeks; (■), 50 weeks.

These studies showed that iodized salt and iodized oil supplementation are effective strategies to eliminate iodine deficiency. The efficacy of iodized peanut oil is higher than that of iodized poppy seed oil. To ensure that all salt is iodized adequately, evaluation of the level of salt iodization in Indonesia is still needed.

Multimicronutrient supplementation

Iron and vitamin A supplementation during pregnancy and nutritional status of infants

Poor nutritional status among infants and children may be due in part to inadequate maternal nutritional status during pregnancy. More than half of the pregnant women in Indonesia suffer from iron deficiency anaemia,[17] and one-third of the pregnant and lactating women suffer from marginal vitamin A deficiency.[18,19] Vitamin A deficiency has been associated with morbidity and mortality and the aetiology of anaemia among children and women.

The effect of weekly iron and vitamin A supplementation during pregnancy on iron and vitamin A status of pregnant women at near term and their infants was investigated in a community-based study in rural areas in Indonesia.[20,21] Women (*n* = 366) from five villages, 16–20 weeks pregnant, aged 17–35 years and with haemoglobin concentrations 80–140 g/L were randomly allocated on an individual basis to receive a weekly supplement either with 120 mg elemental iron and 500 μg folic acid or the same amount of iron and folic acid plus 4800 retinol equivalent (RE) vitamin A. A third group, made up of women who were participating in ongoing national iron supplementation in which women are advised to take iron tablets daily during pregnancy, was recruited at the same time from four neighbouring villages. Supplementation did not significantly improve the iron status but it prevented the decrease of serum retinol concentration in pregnant women. The micronutrient status of pregnant women is shown in Fig. 2. At approximately 4 months of age, infants of mothers supplemented with vitamin A and iron had higher serum retinol concentration than infants of mothers supplemented with iron alone

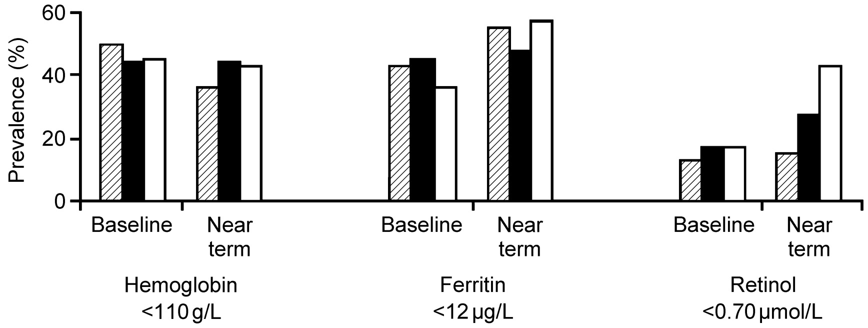

Figure 2. Proportion of pregnant women with anaemia, low iron stores, and marginal vitamin A deficiency in the (▨) weekly vitamin A + iron group; the (■) weekly iron group, and the (□) 'daily' group.[20]

(0.62 ± 0.02 *vs* 0.54 ± 0.02 µmol/L, $P < 0.01$, mean ± SE). Concentrations of haemoglobin and serum ferritin, and weight and length of infants did not differ between groups. These studies also showed that the performance of weekly iron supplementation did not differ from that of the ongoing daily iron supplementation in improving the iron status of women during pregnancy and of their infants. In conclusion, the inclusion of vitamin A in iron supplementation should be considered. Daily iron supplementation during pregnancy needs to be continued beyond parturition provided that the compliance is improved.

Multimicronutrient supplementation and growth of children

One of the consequences of micronutrient deficiencies among children is growth retardation. Many preschool children in developing countries suffer from micronutrient deficiency. When the prevalence of anaemia is high (>40%), it is assumed that the prevalence of zinc deficiency is also high. In addition to deficiencies in iron and zinc, many preschool children are vitamin A-deficient as well.

The efficacy of multimicronutrient supplementation administered daily or weekly was investigated among preschool children aged 6–24 months in Vietnam.[10] Children were supplemented with 8 mg elemental iron, 5 mg elemental zinc, 333 µg retinol and 20 mg vitamin C 5 days per week (daily group; $n = 55$); or with 20 mg elemental iron, 17 mg elemental zinc, 1700 µg retinol and 20 mg vitamin C once per week (weekly group; $n = 54$); or with placebo (placebo group; $n = 54$). Supplementation was given for 12 weeks. At baseline, the prevalence of anaemia (haemoglobin concentration <110 g/L) was 46%, zinc deficiency (serum zinc concentration <10.71 µmol/L) was 36%, and vitamin A deficiency (serum retinol concentration <0.70 µmol/L) was 46%. Concentrations of haemoglobin and serum zinc and retinol concentration increased significantly in the daily and weekly groups but not in the placebo group. Supplementation also reduced the prevalence of micronutrient deficiencies significantly. In the overall population, growth was not affected by supplementation. However, both daily and weekly supplementation did improve the growth of stunted children.

Multimicronutrient supplementation and work performance

Anaemia is related to work output as regards both heavy labour and less physically strenuous occupations. It is generally accepted that more than 50% of anaemia cases are due to iron deficiency. Other micronutrient deficiencies such as that of vitamin A, riboflavin, and vitamin B12 may result in anaemia. An earlier study among female cigarette rollers ($n = 230$) showed that anaemic subjects rolled cigarettes 4.9% less ($P < 0.01$) than their non-anaemic counterparts.[22] Hence, it is hypothesized that multimicronutrient supplementation could effectively increase work productivity.

Shoe factory female workers in the sewing department, non-pregnant and non-lactating ($n = 308$), were allocated randomly to three groups to receive a supplement 5 days per week for 12 weeks.[23] The multimicronutrient group received a supplement containing 5000 IU vitamin A, 60 mg vitamin C, 1.5 mg thiamine, 1.7 mg riboflavin, 20 mg niacin, 400 IU vitamin D, 30 IU vitamin E, 2 mg vitamin B6, 0.4 mg folic acid, 6 µg vitamin B12, 10 mg pantothenic acid, 27 mg elemental iron, 450 mg (elemental) calcium and 15 mg zinc (Bayer; Elkhart, USA). The weekly iron group received 60 mg elemental iron and 0.25 mg folic acid supplement once per week and placebo on four other days (Phapros, Indonesia). The placebo group received placebo 5 days per week (PT Kimia Farma). On average, the subjects were 22 ± 3 years old (mean ± SD), had a bodyweight of 46 ± 6 kg, height of 150 ± 5 cm, and body mass index of 20.3 ± 2.3 kg/m^2.

Twelve weeks after supplementation, the haemoglobin and serum retinol concentrations in the multimicronutrient group were significantly higher than those in the placebo group. Both multimicronutrient and iron–folic acid supplementation increased serum ferritin concentrations significantly (Table 1). Multimicronutrient or iron–folic acid supplementation significantly improved the work productivity in a similar fashion. In conclusion, multimicronutrient supplementation had a better impact on haematological status compared to iron–folic acid supplementation. Both multimicronutrient and iron–folic acid supplementation had a similar impact as regards increasing work productivity.

Vitamin A and zinc supplementation and tuberculosis

Tuberculosis (TB), one of the oldest human diseases, is commonly associated with urban settlement and crowded environmental living conditions. It is a chronic infectious disease caused by *Mycobacterium tuberculosis*. Nutrition, such as vitamin A and zinc status, plays an important role in the course of TB. Both vitamin A and zinc have immune function properties.

Table 1. Concentrations of haemoglobin and serum ferritin and retinol before and 12 weeks after supplementation among female factory workers[23]

	Multimicronutrients $n = 3$	Iron $n = 44$	Placebo $n = 45$
Haemoglobin (g/L)			
Before	132 ± 12	129 ± 13	131 ± 14
After	137 ± 12*	132 ± 12	128 ± 15
Serum ferritin (μg/L)			
Before	31.37 ± 20.12	32.71 ± 25.45	25.41 ± 21.44
After	44.82 ± 25.91**	43.98 ± 31.82**	29.69 ± 22.16
Serum retinol (μmol/L)			
Before	1.77 ± 0.56	1.61 ± 0.49	1.86 ± 0.57
After	2.34 ± 0.73 *	2.01 ± 0.72	1.87 ± 0.63
Work productivity (%)†	$n = 100$	$n = 103$	$n = 105$
Week 1	99.3 ± 7.8	99.3 ± 6.8	100.6 ± 7.4
Week 7	102.9 ± 7.8***	105.6 ± 9.0***	100.2 ± 8.0
Week 12	102.1 ± 7.2***	103.7 ± 9.0***	99.9 ± 6.5

†Work productivity was calculated as the weekly average of the percentage of the products made per hour per day in comparison to the target set by the company. The company sets a target to produce a product per hour for each type of work.
*Significantly different from placebo group, $P < 0.01$, ANOVA.
**Significantly different from placebo group, $P < 0.05$, ANOVA.
***Significantly different from placebo group, $P < 0.01$, Wilcoxon sign–rank test.

Newly diagnosed TB patients ($n = 80$) receiving the standard TB treatment following World Health Organization (WHO) guidelines were randomly allocated to either receive supplement daily with vitamin A (5000 IU) together with zinc (15 mg) or placebo for 6 months.[24] Clinical examination, micronutrient status and anthropometric assessment were carried out prior to, and after 2 and 6 months of treatment. The prevalence of being underweight (body mass index <18.5 kg/m^2) was 64%, whereas the prevalence of low vitamin A status (plasma retinol concentrations <0.70 μmol/L) was 32% and that of low zinc status (plasma zinc concentration <10.7 μmol/L) was 30%. Supplementation did significantly increase plasma retinol concentration after 6 months, but did not significantly increase plasma zinc concentration after 2 and 6 months. With respect to disease recovery, the supplemented group had a significantly earlier resolution of X-ray lesion areas and sputum conversion. The effect of supplementation in this study was not particularly large, but the increase in speed of response in the supplemented group could be of considerable public health significance. Therefore, further studies with larger samples on the effect of micronutrient supplementation in TB treatment are required.

Conclusions

Although micronutrients are needed in minute amounts, the consequences of deficiency are enormous. World Bank estimates that micronutrient malnutrition costs national economies up to 5% of gross domestic product (GDP) through death and disability, but the solution would cost as little as 0.3% of GDP.[25] The presented studies show that many population groups in Indonesia and in Vietnam suffer from multimicronutrient deficiencies. Weekly supplementation of multimicronutrient is applicable for prevention of micronutrient deficiencies in children and adult women, although it may not be appropriate in pregnant women. In general, micronutrient supplementations are able to improve the situation, including improvement in work performance and in preventing and curing the diseases. However, the efficacy of supplementation at a research level often cannot be translated directly to effectiveness in a large-scale setting. Lessons learnt from existing community-based nutrition programmes indicate that 'ownership' by the community is fundamental to success, in addition to using a sound approach in programme implementation.[26]

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