Review Article

Micronutrients and growth of children: A literature review

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Abstract

Optimal growth and development in children will be able to be achieved if the nutritional needs can be met. There are many teenagers who are malnourished because of inadequate intake. This study aims to examine the relationship between micronutrient especially folic acid and zinc with growth. The method used is a literature review of various sources of free accredited journals in pdf form eg PubMed, Proquest, Google Scholar and EBSCO. Other sources were such as books, reports national and international health. We collected literature published in the last 10 years to maintain the novelty of information. Some sources of literature were beyond the time limit if those are beneficial to this study. The results of the literature review indicate that there is a relationship between micronutrient and growth but this is still being debated. This study recommends for further follow-up especially on experimental studies in certain age groups.

KEY WORDS: Micronutrients, folic acid, zinc and growth

Introduction

Optimal growth and development in children will be able to achieve if the nutritional needs can be met. However, in reality, there are many teenagers who are malnourished due to inadequate intake and the presence of infectious diseases.[1] Micronutrients, to the attention of many people especially public health experts and nutrition, are directly related to the growth and intelligence. Although, the data deficiency of zinc as an essential part of the micronutrient in Indonesia, for example, seems to be not yet fully available, but need to be aware of this possibility prevalence of zinc deficiency. A study conducted in the northeastern province of Thailand showed that about 70% of school children have low zinc levels and potentially affect their academic ability and growth.[2,3] Furthermore, the lack of zinc can provide a wide range of impacts e.g. somatic growth of children and endocrine systems as well as inhibition of sexual maturation, hypogonadism, and thyroid dysfunction.[4]

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Food and Agriculture Organization has set 4 strategies to solve the problem of micronutrient deficiencies, such as (1) the diversification of food, (2) food fortification, (3) supplementation with vitamins and minerals, as well as (4) the measurement of global public health and disease control.[5] Food fortification is one of the best strategies because it has economic value with a higher level of compliance, so this way is more effective in reducing nutrient deficiency problems. In addition, fortification can also be used as a means of safe and effective way to supplement your diet with a low content of iron. Some countries have made efforts fortification in some products such as flour, oil, soy sauce, noodles, and rice.[6,7]

In Indonesia, rice fortification can be a prospective strategy in addressing micronutrient deficiencies because rice is the main commodity. Almost all of Indonesia's population consumes rice. According to data Susenas in 2013, that the average consumption of rice per day of Indonesia's population reached 263.9 g/person, and not much difference between consumption in urban areas (253.3 g/person/day) and rural (274.4 g/person/day). Currently, the rice is only able to contribute calories but low in micronutrients such as folic acid, vitamin B1, niacin, iron, and zinc. Therefore, through the fortification of rice can provide micronutrient intake when consumed.[8]

Based on the cost estimates by some experts that in addition to iron, which is known cost-effective in the fortification program, folic acid and zinc also has a cost benefit in the fortification program.[9,10] Therefore, fortified by the addition of folic acid and zinc is very feasible. Fortification by considering cost effectiveness can be an effective and efficient way in solving the problem of micronutrients. Based on WHO recommendations, some micronutrients can be included in the rice and the number refers to the cornstarch and flour fortification include iron, folic acid, vitamin B12, vitamin A, zinc, thiamin, niacin, and vitamin B6.

Although, many studies that show the effects of folic acid and zinc on brain development and function, but is still limited to animal studies. Therefore, research and studies in humans remains to be done.

Materials and Methods

This study was a review of the literature. The stage of reference management procedure was gathering information from various relevant sources then grouped according to theme. A literature came largely from an accredited journal providing articles for free in pdf format e.g. PubMed, Proquest, Google Scholar, and EBSCO. Other sources were such as books, reports on national and international health. To maintain the novelty of information, we tried to collect literature published in the last 10 years. Some sources of literature were beyond the time limit for benefits and enriched the results and discussion. The next stage was to study literature to ensure that the step does not go out of the main topic of discussion.

Result and Discussion

This study specifically examined folic acid and zinc in relation to growth

Folic Acid and Growth

In children, chronic anemia can inhibit the growth and long-term impact on the development of neuro, through changes myelinasi neurotransmitter, monoamine metabolism in the stratum, the functioning of the hippocampus, and energy metabolism. Growth and puberty is hampered by the complications of thalassemia. Chronic anemia has a negative effect on linear growth during the growth phase of man (infants, children, and adolescents). In addition, chronic anemia can also cause obstruction in cognitive, psychomotor, and affective in the long term. The mechanism is through a defective secretion of IGF-1. Improvements in anemia may increase the secretion of IGF-1 and reach potential growth.[11]

Sufficient micronutrients such as folic acid, vitamin B12, and vitamin A can prevent chronic anemia.[12,13] Folic acid supplementation is often used as a substance or fortification, and had a lot of evidence showing its benefits to the prevention of anemia. In addition to its effects on anemia, folic acid along with iron would positively impact on growth.[14] The mechanism is the iron–folic acid can increase hemoglobin and hematocrit values. It occurs in people who are given daily or weekly.[14] Different results were obtained in Indonesia, with the iron–folic acid supplementation once a week (60 mg Fe + 0.25 mg folic acid) anemia among young people could significantly improve Hb although not with weight and height during the 5-week intervention.[15] This positive relationship between the additions of hemoglobin with better adolescent growth is explained by an increase in iron requirements during the adolescent growth therefore; total blood volume expansion, increased body mass, as well as the rapid development of skeletal muscle. In addition, iron–folic acid also gave positive results on physical work capacity or psychomotor.[14]

Therefore, the benefits of regular iron–folic acid is not only beneficial to the Hb level but also at the adolescent growth period as well as their cognitive growth spurt.[14,16] The results of the study recommend that the study of efficacy and effectiveness of the administration of iron–folic acid in adolescents to see the impact on the weight and height.[16] Other studies show the effect of iron supplementation of 60 mg + 0.5 mg of folate for 3 months can significantly increase the linear growth. This mechanism, according to Lawless et al.[17] and Kanani and Poojara[18] the increase in growth due to the iron–folate supplementation because of an increase in appetite and subsequent intake.

Several other research results can be seen to compare the link between micronutrient- folic acid and growth as shown in Table 1.

Zinc and Growth

Zinc is the second most abundant element in the body and zinc deficiency has serious effects on normal body physiology.[24] The human body contains about 2 g of zinc. These minerals distributed in the blood, kidney, liver, bone, and brain. Zinc is a cofactor of more than 300 enzymes or metaloprotein. Zinc along with protein plays an important role in the biology of cell mitosis, protein synthesis, synthesis of DNA and RNA. Therefore, zinc plays an essential role in normal growth and development. Prasad in 1961 found that zinc deficiency causes dwarfism with the delay physical and sexual development in humans. Currently, widespread zinc deficiency adversely affect immunologic system, causing adverse effects on body growth and sexual development and affect the smell and taste dysfunction.[25] Other effects can include psychological disorders, anorexia, and movement disorders. Interestingly, all the effects are reversible with the consumption of zinc supplements.[24]

However, based on the results of studies that have been done, the effect of zinc supplementation only gave a small effect on growth. Zinc mediated growth through its influence on the activity of insulin-like growth factor 1 (IGF-1), but it is also important for the synthesis of nucleic acids and proteins that also contribute to the growth and physical development of human beings. The results of this study concluded that zinc in combination with other micronutrients is a better contribution to the growth and only a little effect if zinc is alone.[25] Supported by studies of Silva et al.,[26] the effect of zinc supplementation on growth alone is not better than the control.

Table 1: Micronutrient-Folic Acid and Growth

Author (Year)	Aim	Findings
Haider et al.[19]	To evaluate the evidence of the impact of multiple micronutrient supplements during pregnancy, in comparison with standard iron-folate supplements, on specific maternal and pregnancy outcomes of relevance to the Lives Saved Tool (LiST).	There was no significant benefit of multiple micronutrients as compared to iron folate on maternal anemia in third trimester [Relative risk (RR) = 1.03; 95% confidence interval (CI): 0.87–1.22 (random model)]. Our analysis, however, showed a significant reduction in SGA by 9% [RR = 0.91; 95% CI: 0.86–0.96 (fixed model)]. In the fixed model, the SGA outcome remained significant only in women with mean body mass index (BMI) ≥ 22 kg/m^2. There was an increased risk of neonatal mortality in studies with majority of births at home [RR = 1.47, 95% CI: 1.13–1.92]; such an effect was not evident where ≥ 60% of births occurred in facility settings [RR = 0.94, 95% CI: 0.81–1.09]. Overall there was no increase in the risk of neonatal mortality [RR = 1.05, 95% CI: 0.92–1.19 (fixed model)].
Khan et al.[20]	To evaluate the effects of prenatal food and micronutrient interventions on postnatal child growth.	There were no differences in characteristics of mothers and households among the different intervention groups. The average birth weight was 2694 g and birth length was 47.7 cm, with no difference among intervention groups. Early invitation to food supplementation (in comparison with usual invitation) reduced the proportion of stunting from early infancy up to 54 months for boys ($p = 0.01$), but not for girls ($p = 0.31$). MMS resulted in more stunting than standard Fe60F ($p = 0.02$). There was no interaction between the food and micronutrient supplementation on the growth outcome.
Baruaet al.[21]	To discuss the role of FA in human health and to review the benefits, concerns, and epigenetic effects of maternal FA on the basis of recent findings that are important to design future studies.	The clinical application of FA supplementation/intake to prevent NTDs has been well proven for the last 20–25 years. However, considering the concern with the level of folate concentration following post-fortifications, it is of interest to explore if FA exposure in significant sections of the population is influencing other normal biological processes, such as the brain's development.
Khot et al.[22]	To prove the hypothesize that an imbalance in the levels of maternal micronutrients (folic acid, vitamin B12) during pregnancy will differentially program the expression of genes encoding critical enzymes (expressed by mRNA levels) involved in the one carbon cycle (described earlier in Figure 1), and omega-3 fatty acid supplementation may prevent some of these changes.	Results suggest that maternal micronutrient imbalance (excess folic acid with vitamin B12 deficiency) leads to lower mRNA levels of methylene tetrahydrofolate reductase (MTHFR) and methionine synthase , but higher cystathionine b-synthase (CBS) and phosphatidylethanolamine-N methyltransferas (PEMT) as compared to control. Omega-3 supplementation normalized CBS and MTHFR mRNA levels. Increased placental phosphatidylethanolamine (PE), phosphatidylcholine (PC), in the same group was also observed.
Lu et al.[23]	To evaluate the effect of maternal multi-micronutrient supplementation on postnatal growth of children under 5 years of age.	Antenatal multi-micronutrient supplementation has a significant positive effect on head circumference of children under 5 years. No impact of the supplementation was found on weight, height, WAZ, HAZ, and WHZ.

Very small effect is likely due to the small sample size, short intervention period, or because their micronutrient deficiencies since the beginning.

Several other research results can be seen to compare the link between micronutrient- zinc and growth as shown in Table 2.

Conclusion and Recommendation

The results of the literature review indicate that there is a relationship between micronutrients and growth but this is still being debated. This study recommends for further follow-up especially on experimental studies in certain age groups.

Table 2: Micronutrient-zinc and growth

Author (Year)	Aim	Findings
Chhagan et al.[27]	To ascertain whether adding zinc or multiple micronutrients to vitamin A supplementation improves longitudinal growth or reduces prevalence of anemia in children aged 6–24 months.	Among all children, there were no significant differences between intervention arms in length-for-age Z scores (LAZ) changes over 18 months. Among stunted children (LAZ below -2) [n = 62], those receiving MM had a 0.7 Z-score improvement in LAZ versus declines of 0.3 in VAZ and 0.2 in VA (p = 0.029 when comparing effects of treatment over time). In the 154 HIV-uninfected children, MM ameliorated the effect of repeated diarrhea on growth. Among those experiencing more than 6 episodes, those receiving MM had no decline in LAZ compared to 0.5 and 0.6 Z-score declines in children receiving VAZ and VA, respectively (p = 0.06 for treatment by time interaction). After 12 months, there was 24% reduction in proportion of children with anemia (hemoglobin below 11 g/dL) in MM arm (p = 0.001), 11% in VAZ (p = 0.131) and 18% in VA (p = 0.019). Although the within arm changes were significant; the between group differences were not significant. Daily multiple micronutrient supplementations combined with vitamin A was beneficial in improving growth among children with stunting, compared to vitamin A alone or to vitamin A plus zinc.
Imdad and Bhutta[28]	The results of previous meta-analyses evaluating effect of zinc supplementation on linear growth are inconsistent. This review have updated and evaluated the available evidence according to grading of recommendations, assessment, development and evaluation (GRADE) criteria and tried to explain the difference in results of the previous reviews.	Zinc supplementation has a significant positive effect on linear growth, especially when administered alone, and should be included in national strategies to reduce stunting in children < 5 years of age in developing countries.
Tidemann-Andersen et al.[29]	To study the iron and zinc content of the key food items in the diet of primary school children in Kumi district of Uganda.	The school children of Kumi district had a predominantly vegetable based diet. Foods of animal origin were consumed occasionally. The iron content in the selected foods was high and variable, and higher than in similar ingredients from Kenya and Mali, while the zinc concentrations were generally in accordance with reported values. The total daily zinc (mg) intake does not meet the daily RNI. The iron intake is adequate according to RNI, but due to iron contamination and reduced bioavailability, RNI may not be met in a vegetable based diet.
Abass, Hamdan[30]	To Measure Zinc and copper levels in low birth weight deliveries in Medani Hospital, Sudan	The two groups (50 in each arm) were well matched in their basic characteristics. Median (25–75th interquartile range) maternal zinc (62.9 [36.3–96.8] vs. 96.2 [84.6–125.7] µg/dl; P <0.001) and copper (81.6 [23.7–167.5] vs. 139.8 [31.9–186.2] µg/dl; P = 0.04) levels were significantly lower in cases than in controls. Cord copper levels in cases were significantly lower than those in controls (108 [55.1–157.9] vs. 147.5 [84.5–185.2] µg/dl; P = 0.02). There were significant direct correlations between birth weight and maternal copper levels and maternal and cord zinc levels. Maternal zinc and copper levels, as well as cord copper levels, are lower in LBW newborns than in those with normal weight.

Sadeghi et al.[25]	To present data from the association of plasma zinc, copper and toxic elements of lead and cadmium levels with bone mineral density in Iranian women.	No differences were found in the nutritional status, number of diseases, drugs, and functional activities between these groups. Plasma Zn, Cu, Pb, Cd levels were analyzed by, a method of voltammetry. Mean ± SD levels of copper and zinc was 1.168 ± 0.115, 1.097 ± 0.091 µg/ml in control group, 1.394 ± 0.133, 1.266 ± 0.11 µg/ml in total patient (TP) and 1.237 ± 0.182, 1.127 ± 0.176 µg/ml in mild patients (–1 > T-score >–1.7), 1.463 ± 0.174, 1.327 ± 0.147 µg/ml in severe patient group (T-score <–1.7); respectively. Mean ± SD plasma level of lead and cadmium was 168.42 ± 9.61 ng/l, 2.91 ± 0.18 ng/ml in control group, 176.13 ± 8.64 ng/l, 2.97 ± 0.21 ng/ml in TP, 176.43 ± 13.2 ng/l, 2.99 ± 0.1 ng/ml in mild patients, 221.44 ± 20 ng/l and 3.80 ± 0.70 ng/ml in severe patient group, respectively. In this study plasma zinc, copper, lead, and cadmium concentrations were higher in the patients than in the control, though differences were not significant. However, differences were higher between the controls and patients with severe disease (T-score <–1.7). In addition adjusted T-score of femur with age and BMI showed negative significant correlation with plasma levels of zinc and lead in total participants ($p < 0.05$, $r = -0.201$, $p = 0.044$, $r = -0.201$).
Shaikhkhalil et al.[31]	To evaluate the effect of enteral zinc supplementation on weight gain and linear growth in ELBW infants with CLD who received volume-restricted fortified human milk.	Zinc supplementation started at postmenstrual age 33 } 2 weeks. Most infants received fortified human milk. Weight gain increased from 10.9 before supplementation to 19.9 g kg–1 day–1 after supplementation (p < 0.0001). Linear growth increased from 0.7 to 1.1 cm/week ($p = 0.001$). Zinc supplementation improved growth in ELBW infants with CLD receiving human milk. Further investigation is warranted to re-evaluate zinc requirements, markers, and balance.

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