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Meeting Micronutrient Requirements for Health and Development: An Update

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Introduction

Despite numerous advances and improvements in child health, malnutrition still remains as one of the main public health challenges of the 21st century, particularly in developing countries [1]. It undermines the survival, growth and development of children and is associated with almost 35% of all deaths in children under the age of five worldwide.[2] An estimated 178 million children are stunted globally and an additional 19 million children have severe acute malnutrition (wasting).[2] Any of these conditions are associated with concomitant micronutrient deficiencies. Among these: vitamin A, Iron, Zinc and Iodine deficiencies are the most prevalent in childhood and vitamin A and zinc deficiency associated with an estimated one million child deaths and 9% of global childhood DALYs (Disability-Associated Life years)[2]. Recent data on the timing of growth retardation and stunting in infants suggest that the onset is commensurate with inappropriate complementary feeding and potentially compounded by maternal undernutrition and intrauterine growth retardation (IUGR), and that the first 24 months represent a critical window of opportunity for intervention[3]. The relationship between micronutrient deficiencies and increased risk of infections and mortality is well established [4]. Several micronutrients play important role in the immune system and are critical in determining the outcome of host microbe interactions [5] Infections on the other hand are a risk factor for malnutrition as during an episode of an infection, there is a general decrease in nutrients intake, increase losses (e.g. G.I losses, fluid losses etc.) and altered metabolic pathways. This condition is more prevalent among poor children whose micronutrient status is already marginal and they also have high frequency of infectious disease. This leads to a vicious cycle where malnutrition is a health outcome as well as a risk factor for disease and exacerbation of malnutrition[6]. The resulting complex and mutually adverse interactions with infections constitute the major determinants of childhood morbidity and mortality among the underprivileged preschool children in several developing countries[7]. The purpose of this paper was to summarize the current knowledge on micronutrient deficiencies and their role in reducing morbidity and mortality during childhood.

Vitamin A

Vitamin A has been termed as an anti-infectious agent plays an important role in visual system.[8] Vitamin A deficiency (VAD) impairs numerous body functions and can lead to many adverse health consequences including xerophthalmia (dry eyes), infections, morbidity, mortality, sub-optimal physical growth and anemia[8]. VAD is a major nutritional public health problem in the developing world. According to the latest report of the WHO, globally about 190 million preschool-aged children and 19.1 million pregnant women are vitamin A deficient (i.e. serum retinol < 0.70 ìmol/l)[9]. This corresponds to 33.3% of preschool-aged children and 15.3% of pregnant women in populations at risk of VAD. According to current estimates, 122 countries are classified as having a moderate to severe public health problem based on biochemical VAD in preschool-aged children, and 88 countries based on biochemical VAD in pregnant women[9]. Xerophthalmia, resulting from VAD is the primary preventable cause of blindness and of the world's children with xerophthalmia, nearly half reside in South or South-East Asia, of whom more than 85% live in India[10]. About 5.2 million preschool-aged children and 9.8 million pregnant women suffer from night blindness, which represents 0.9% and 7.8% of the population at risk of VAD, respectively. The estimates show that Africa and South-East Asia contain the highest proportions of preschool-aged children and pregnant females with biochemical VAD and night blindness[9]. Evidence from community trials has shown that vitamin A supplementation (VAS) reduces all-causes of mortality and diarrhea and measles specific mortality[11]. It also reduces incidence of measles and diarrhea infection[11]. VAS has also been shown to reduce prevalence of xerophthalmia and night blindness[11]. VAS as an adjunct in the treatment of measles has been shown to reduce

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mortality, pneumonia-specific mortality and incidence of croup[12]. World health organization recommends two annual high-dose supplements of vitamin A for every child at risk of VAD [13]. Since 1998, large vitamin A supplementation programs are in place in about 193 UNICEF targeted countries to deliver the required dose of vitamin A[14]. It can be noted that in 1999, just 16% of children in these countries received full vitamin A supplementation while in 2005 this number increased to 72% [15].

Vitamin A supplementation:

The WHO recommends VAS for young children at a dose of 50,000 IU for infants <6 months of age, 100,000 IU for infants 6-12 months of age and 200,000 IU for children over 12 months of age, every 4 to 6 months (WHO 1997)[16]. The international community, recommends for a target of all children between the ages of 6 months and 5 years, in all countries where over 70 in 1,000 children die before the age of 5, as this is the internationally accepted proxy to indicate that vitamin A deficiency is a public health problem[17]. However, worldwide, a large proportion of children receiving it are neither vitamin A deficient nor stunted nor wasted. The effect of such a public health policy on this population needs to be carefully assessed.

Mortality outcomes: VAS in > 6 month old children

In Indonesian children who received massive dose of vitamin A supplements, had a 34 percent lower mortality from all causes than those not receiving the supplement[18]. A meta analysis of these initial studies concluded that VAS to measles hospitalized patients was highly protective for mortality. And, when given periodically to children at the community level, it decreased overall mortality[19].

Mortality outcomes: Children 1-5 months of age

Studies where children were supplemented with vitamin A between 1 and 5 months of age did not show any positive effect on overall mortality[20]. Plausible explanations for these findings have focused on differences in environmental influences on this age group in relation to older infants (e.g. the protection of breast feeding against malnutrition and infection) Whether this could be explained by the interactions with vaccines given at this age, such as inactivated DTP vaccine, with vitamin A need to be further investigated

Vitamin A in newborns

In developing countries, infants are born with low stores of vitamin A and depend on external sources. Sometimes breastfeeding is not enough and newborns and infants need VAS; however, results obtained with this strategy have been contradictory. Studies from Bangladesh[21], India[22], and Indonesia[23], have shown reductions in all-cause mortality (15%, 22% and 63%, respectively) in infants who received VAS relative to controls. Also, VAS has shown to reduce diarrhea case–fatality rates and the incidence of fever[24]. One study performed in Nepal showed no overall effect on early infant mortality and there was a tendency for the relative risk of mortality among vitamin A recipients to rise with improved nutritional status[25]. Trials in Africa, in countries like Guinea-Bissau[26], and Zimbabwe[27] suggest a lack of benefit from vitamin A supplementation. Many speculations have been so far formulated in order to understand these controversial results. A recent meta regression analysis performed by Rotondi et al[28], suggests that vitamin A supplementation to neonates within the first two days of life may confer benefit, specially in regions where the prevalence of vitamin A deficiency is 22% or more among pregnant women. This is an important finding given the current debate as to whether giving neonates vitamin A supplements helps reduce infant mortality in populations where endemic vitamin A deficiency and high infant mortality exist. However, not all neonatal VAS trials support a strong association between vitamin A status and baseline infant mortality, and the VAS effect. Thus, in the Indonesian trial mothers had a good vitamin A status and infants a very good effect of VAS[10].

Morbidity outcome: Diarrhea, LRTI and measles

In relation to morbidity, another controversy arises: to what extent is the decrease in mortality due to reduction in morbidity from diarrhea and respiratory infection (other than measles). One study in India, with measles vaccinated and not severely malnourished children, concluded that VAS did not reduce respiratory and diarrheal morbidity as compared to the placebo controls[29].

Even more controversial, VAS has been shown, not only not be beneficial, but detrimental in pediatric population. In a blinded, randomized controlled trial (RCT) performed in Mexico[30], where measles vaccination coverage is very high and mortality in children < 5 years has been estimated in 17.4/1000

live births (2009) (Information from DGIS, SS Mexico), VAS to infants 6-15 mo was associated with a 27% increase in diarrheal disease and a 23% increase in cough with fever. The authors postulated that the increase in diarrhea in this study might reflect the effect of VAS to down-regulate the Th1 response, which protects against rotavirus. Similarly, they speculated that negative respiratory outcomes might be explained by the adverse effect of VAS in respiratory syncytial virus infections[31]. A meta analysis by Chen et al[32] concluded that VAS does not have a universal protective effect as prophylaxis for LRTI in children; indeed, three studies showed an increase in respiratory morbidity associated with VAS.

Folate and vitamin B12: function and importance in cognitive development

Biochemical Function of Folate and Vitamin B12:

The importance of folate and vitamin B12 for healthy neurological development and function is unquestioned. As essential co-factors for one-carbon metabolism, folate and vitamin B12 are required for biological methylation and DNA synthesis. Methylation activity is essential for many processes that are critical for central nervous function, such as the epigenetic regulation of gene expression by DNA and histone methylation, the methylation of myelin basic protein and membrane phosphatidylcholine, the synthesis of hormones and neurotransmitters such melatonin and epinephrine, and the inactivation of dopamine and catecholamines. Folate (in the form of 5-methyltetrahydrofolate) and vitamin B12 are required in all tissues to maintain adequate cellular methionine, which in turn is converted to S-adenosylmethionine (SAM) the universal methyl-donor for these reactions. Folate and B12 deficiency inhibit methylation and cause homocysteine to accumulate in circulation. Homocysteine may be cytotoxic and mildly elevated plasma homocysteine is associated with increased risk of neurodegnerative and cardiovascular disease. By increasing choline utilization or by depleting membrane phosphatidylcholine, folate deficiency might also indirectly limit the synthesis of the key neurotransmitter acetylcholine. Folate is needed to synthesize thimidylate and purine nucleotides. Thus, folate deficiency can compromise DNA replication and integrity. Vitamin B12 serves as a coenzyme for methylmalonyl-CoA mutase which catalyzes the final step in the mitochondrial degradation of odd chain fatty acids and branched amino acids. These biochemical effects of deficiency can be theoretically linked to the observed neuropathological, cognitive and developmental abnormalities that are associated with deficiency of these vitamins[33].

Neurological consequences of acquired and congenital defects in one-carbon metabolism

The importance of folate and vitamin B12 for healthy brain development and function is evident. Severe acquired deficiencies of vitamin B12 and folate manifest with either haematological or neurological abnormalities or a combination of both[34]. The primary neurological feature is a progressive neuropathy in which sensation and motor control are gradually lost, typically beginning with the lower limbs[35]. In addition, these conditions are often accompanied by behavioral changes ranging from mild irritability to severe depression, hallucinations, confusion and memory loss[36].

Symptoms of clinical deficiency can be treated with intramuscular injections and high dose oral supplementation, leading to hematologic and neurologic recovery; however in the long term, resolving the deficiency and acute pathology does not guarantee full restoration of cognitive development[37].

Sub-clinical deficiencies in CNS development and aging

The neuropathology common to both congenital and severe acquired vitamin B12 and folate deficiencies include increased risk of neural tube defects (NTDs) among children born to mothers with low folate status, and increased risk of cognitive impairment, depression, Alzheimer's disease and stroke among older adults.

With respect to aging, the association between low B-vitamin status and increased risk of neurodegenerative disease has been extensively reviewed[38]. Data from over 100 observational cross sectional and prospective studies, encompassing over 50,000 subjects in total, provides compelling evidence for the association with approximately 90% of the studies reporting significant associations and the remainder not. Taken together, they provide the basis for the tenable hypothesis that "low-normal intake or blood concentrations of B-vitamins (folate, B12 and B6) and/or moderately elevated plasma total homocysteine increase the risk of brain atrophy and developing cognitive impairment in the elderly[33,38]. Early observations that poor folate status is associated with increased risk of spina bifida and anencephaly led to highly successful clinical trials in which use of

periconceptual folic acid supplements reduced the risk of incident NTDs by as much as 50 percent or more[39].

Folate and B12 supplementation and cognitive development

The upper limit of folate intake for adults was conservatively set at 1 mg per day out of concern for the possibility that in individuals with frank B12 deficiency, high folate might either exacerbate the symptoms or "mask" the associated anemia, delaying early detection and treatment and thus allowing it to progress. Cross sectional data from the NHANES and SALSA cohorts show that the metabolic effects of vitamin B12 deficiency are more pronounced in adults with high folic acid intake. Irrespective of B12 status, high folic acid intake has also been observed to associate with more rapid cognitive decline in older adults and with decreased immune function in older post-menopausal women[40,41].

Iron

Iron is an essential mineral for human development and function. It is required for Hemoglobin and is critical for motor and cognitive development in childhood, and for physical activity in all humans[42]. Iron is also critical to the health of a pregnant mother and her unborn child. A woman needs more iron during pregnancy because the fetus and placenta both need additional iron. Iron supplementation during pregnancy, lowers the risk of maternal mortality due to haemorrhage, the cause of more than 130,000 maternal deaths each year[14]. Supplementation also helps to lower the risks of premature birth and low birth weight. Studies have shown that infants with anaemia caused by iron deficiency have lower mental scores and lower motor scores than infants without anaemia[43].

The influence of inflammatory disorders and infection on iron absorption and the efficacy of iron fortified foods

Introduction

Approximately 90% of daily iron needs can be met by the re-utilization of red cell iron after the breakdown of circulating red cells at the end of their natural life span. Although there is no physiological mechanism for active iron excretion from the body, there are obligatory iron losses from skin, intestine and urinary tract and additional losses during menstruation in women of child bearing age. To maintain iron balance, obligatory and menstrual iron losses, plus the iron required for growth in infants, children, and adolescents must come from the diet. This represents about 1-2 mg of absorbed iron per day. Many young women, infants and children fail to meet their iron needs from diet and these population groups make up the majority of the 2 billion people worldwide estimated to be iron deficient[44]. The situation is worse in the developing world due to low iron bioavailability from plant based diets and iron deficiency has more serious negative health and economic consequences including poor pregnancy outcome, poor cognitive development in children, and decreased physical performance and productivity[45].

Iron fortified foods often contain inhibitors of iron absorption such as phytic acid and polyphenols in cereal and legume foods[46] and calcium in milk products[47]. In order to overcome the negative effects of these inhibitors, the food manufacture usually adds ascorbic acid, although NaFeEDTA and phytase can also be added[48].

There is an inverse correlation between iron status and iron absorption[49] with a 50% decrease in iron stores doubling of iron absorption, although the magnitude of the inhibitory or enhancing effects are independent of iron status. Genetic disorders, nutritional deficiencies, infection and inflammation can also influence iron absorption[50]. Vitamin A deficiency can influence several stages of iron metabolism and riboflavin deficiencies may decrease iron incorporation into hemoglobin. Chronic inflammation[51] and obesity[52] increase hepcidin expression and would be expected to decrease iron absorption[53].

Iron metabolism during infection and inflammation

Iron needed for new red cell synthesis and for replenishing iron enzymes and myoglobin is transported to the bone marrow or body tissues via transferrin in the plasma. The passage of iron into the plasma is mediated via the transport protein ferroprotein situated on the cell membrane[54] and its entry is strictly controlled by the regulatory hormone, hepcidin. This protein is secreted by the liver when iron status is adequate and inhibits the transport of iron into the plasma from both the macrophages and the intestinal cells[55]. Hepcidin binds ferroprotein at the cell membrane, causing internalization and degradation[56] and when iron status is low, hepcidin release from the liver is decreased and iron absorption is maximized.

The innate immune response to microbial infection is to increase hepcidin via an inflammatory response and to restrict microbial growth by restricting the entry

of iron into the plasma[57]. The anemia of infection results from an interruption in the recycling of red cell iron. Macrophage iron is not released resulting in insufficient iron for erythropoiesis. The outcome of many infectious diseases depends on preventing the invading pathogen from obtaining its iron supply, and provision of high iron doses to an infected patient can worsen the infection. In addition to preventing iron release from the macrophage, the inflammatory response would also be expected to prevent iron release from the mucosal cell and thus restrict iron absorption.

Obesity and overweight in relation to iron absorption and the efficacy of iron fortified foods

American national surveys have consistently shown that overweight toddlers, children, adolescents and adults are more likely to be iron deficient than their normal weight counterparts and recent evidence suggests that adiposity related inflammation may play a central role through its regulation of hepcidin[52]. In a recent Swiss study, overweight children were reported to consume similar amounts of bioavailable iron as normal weight children but have a lower iron status, higher serum hepcidin and higher subclinical inflammation as measured by IL-6 and C-reactive protein (CRP)[58].

Zinc

Zinc is the second most abundant transition metal in humans after iron. It is an essential part of about 100 specific enzymes and also serves as structural ions in transcription factors[59].The association of zinc deficiency in children with growth retardation and hypogonadism was first described in 1963 from Iran[60] and it is now well established from animal and human studies that zinc plays a critical role in cellular growth, cellular differentiation and metabolism[61] and in turn promotes immunity, resistance to infection, and the growth and development of the nervous system[60]. Although zinc deficiency is increasingly being recognized as a widespread problem, there is very limited nationally representative data on the magnitude and severity of this deficiency[62]. Some of this is due in part to the lack of reliable biomarkers of zinc status. Recently, Wuehler et al., using data from national food balance sheets compiled by the Food and Agricultural Organization, estimated that 20 % of the world's population is at risk of low zinc intakes[63]. The global prevalence of low intakes by region indicates that 26 % of population in South Asia and 28 % in Sub-Saharan Africa are at risk deficiency[64]. Therapeutic zinc supplementation as an adjunct in the treatment of diarrhea has been shown to reduce the duration of acute diarrhea by 0.5 days and that of persistent diarrhea by 0.68 days. Preventive zinc supplementation reduces incidence of diarrhea by 20 % and that of pneumonia by 15 %[65]. Preventive zinc supplementation has been shown to reduce rate of stunting as well[66]. In 2004, WHO and UNICEF formulated a new recommendation to administer zinc for 10 to 14 days as an adjunct treatment for diarrhea, along with low-osmolarity oral rehydration solutions (ORS) and continuation of feeding[67]. Since then WHO and UNICEF in collaboration with USAID and Johns Hopkins University has worked to ensure the availability of zinc products[68] and about 91 million tablets had been provided in year 2008[69]. Despite all these efforts zinc supplementation is not part of national programs around the globe. Only 46 countries have adopted zinc policy as part of their national child health policy[70]. It is therefore required to scale up the zinc supplementation and it should be incorporated into national diarrhea management policy.

Iodine

Iodine is the key element required for thyroid hormone synthesis, and is also important for brain development during fetal and early years of life[70]. Children born to iodine-deficient mothers may appear normal at birth but might have suffered brain damage and loss in IQ points, affecting their ability to develop to their full potential. These seemingly normal children will later have difficulty learning in school and staying in school. It has been shown that in communities where iodine intake is sufficient, average IQ is shown to be on average 13 points higher than in iodine deficient communities[70]. According to an estimate about 2 billion people have insufficient iodine intake around the globe and about 31.5% of school-age children (266 million) have insufficient iodine intake[71]. Salt iodization is one of the exemplary success stories of food fortification offering great benefits for the intellectual health of nations that have embraced it[72]. Thirty-four developing countries have achieved the universal salt iodization goal, and an additional 38 countries are considered 'on track' for elimination of iodine deficiency disorders[72]. Despite this progress, many countries are lagging far behind. Twenty-four countries have experienced no growth in coverage rates or have even experienced a decline since the mid-1990s[72].

Intervention Strategies to Address Multiple Micronutrient Deficiencies in Early Childhood

Introduction

Micronutrient deficiencies are widespread and are a major global health problem worldwide[73]. World Health Organization (WHO) estimates that more than 2 billion people are deficient in key vitamins and minerals, particularly vitamin A, iodine, iron and zinc. Most of these people live in low income countries and are typically deficient in more than one micronutrient.[74] Globally, about 1.62 billion people are anemic with the highest prevalence in preschool age children (47%) and the second highest in pregnant women (42 %). According to the latest report of the WHO, globally about 190 million preschool-aged children and 19.1 million pregnant women are vitamin A deficient (i.e. serum retinol < 0.70 ìmo l/l)[75]. Approximately 100 million women of reproductive age suffer from iodine deficiency[76]. An estimated 82% of pregnant women worldwide have inadequate intakes of zinc to meet the normative needs of pregnancy[77]. Suboptimal vitamin B6 and B12 status has been observed in many developing countries[78].

Maternal Micronutrient Supplementation during Pregnancy

In 1999 the UNICEF/WHO/UN University proposed a prenatal supplement UNIMAPP containing fifteen micronutrients, including iron and folic acid which could provide one recommended daily allowance of each and potentially replace standard iron-folate supplements for pregnant women in low and middle income countries. A Cochrane review on the subject[81] indicated that compared to iron-folate, multiple micronutrient supplementation had comparable effect on maternal anemia and had a significant effect on incidence of low birth weight (LBW) babies and that of small for gestational age babies

Multiple micronutrient supplementation among children at risk of deficiencies

As deficiencies of important micronutrients like iron, zinc vitamin A etc. are prevalent in children in developing countries, efforts have been made to supplement infants and children with multiple micronutrients. A review by Ramakrishnan et al[81]. based on 20 randomized trials, has shown that multiple micronutrient interventions improved linear growth. Another review by Allen et al[80]. has shown that in children, MMN interventions resulted in small but significantly greater improvements in length or height and weight, hemoglobin), serum zinc serum retinol and motor development. In addition to these benefits, multiple micronutrients have a beneficial effect on mental development of children. A review by Eilander et al.[82] has shown that MMN supplementation during childhood has a significant effect on academic

Conclusions

Micronutrients like vitamin A, Vit B12, foliccid, iron, zinc and iodine are important for growth and survival of children. Given the wide prevalence of multiple micronutrient deficiencies in malnourished children in developing countries, the challenge is to implement intervention strategies that combine appropriate infant and young child feeding with micronutrient interventions at scale. Emerging data from community intervention trials now provide evidence that this is both tangible and can lead to alleviation of childhood under nutrition. Multiple micronutrients supplementation during pregnancy and early childhood in populations at risk is an effective way of prevention of micronutrient deficiencies. Further studies are needed on cost effectiveness and delivery strategies in health system settings.

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