Micronutrient Deficiencies: New solutions to a seemingly irresolvable problem

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Micronutrient deficiencies remain an enormous global problem constituting the 'hidden hunger' leading to poor growth, anemia, developmental delays, blindness and even death. Interventions have had some success in reducing the incidence of iodine and Vitamin A deficiency disorders. However, they have had little global impact on the prevalence of iron and zinc deficiencies. Furthermore, micronutrient deficiencies rarely occur in isolation. Multiple micronutrient deficiencies are relatively common, but most current interventions target only one or two micronutrients.

In light of these ongoing problems, novel therapies are called for that provide multiple micronutrients in a form that is inexpensive, largely self-sustaining, economically viable and most importantly acceptable to the target population. We will review the global importance of micronutrient deficiencies and discuss some of the newer strategies to prevent or treat them.

Global Importance of Micronutrient Deficiencies

Micronutrient deficiencies remain significant global problems, despite many intervention efforts. The Food and Agricultural Organization of the United Nations reports that at least two billion people worldwide, or 33% of the world population, suffer from micronutrient deficiencies.[1] The result is a detrimental health problem that can directly affect intellectual potential and indirectly impact productivity and national development, particularly devastating problems in developing countries.

The most common deficiencies are Vitamin A deficiency (VAD), iodine deficiency disorders (IDD), iron deficiency

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(ID) and the associated anemia (IDA) and zinc deficiency (ZN-def). Together with other vitamin and mineral deficiencies, including selenium, Vitamin C and folate, they constitute the 'hidden hunger,' a term that distinguishes this form of malnutrition from protein-energy malnutrition (PEM).

Vitamin A Deficiency

Vitamin A deficiency (VAD) is the leading cause of preventable blindness in children in developing countries.[2] Between 100 and 140 million children are Vitamin A deficient. Of these, 250,000 to 500,000 children become partially or totally blind each year as a direct result of vitamin A deficiency, and half of them die within twelve months of losing their sight.[3] While clinical VAD with overt visual defects is declining, subclinical VAD is an increasing concern. Although it does not pose a risk to vision, VAD leads to poor growth, weight loss, increased infection, low hemoglobin concentrations and even death.[2,4]

Iodine Deficiency Disorders

Iodine deficiency disorders (IDD), the most common endocrine disorder worldwide, are also the leading causes of preventable brain damage and mental retardation. IDD have a wide range of symptoms ranging from simple goiter, characterized by an enlargement of the thyroid gland, to cretinism, an irreversible form of mental retardation. IDD can also cause impaired physical development and increased infant mortality. About 740 million people worldwide are affected by goiter, and over two billion people are estimated to be at risk of IDD, particularly those living in countries where the soil and water iodine content are low such as India, Nepal and China.[5-6]

Iron Deficiency and Anemia

Iron Deficiency (ID) is the most prevalent nutritional deficiency worldwide, primarily affecting individuals living in developing countries. It defines a spectrum of diseases ranging from iron depletion (where iron stores are mobilized to make up for inadequate dietary intake), to non-anemic iron deficiency (where the availability of iron begins to limit hemoglobin synthesis), to iron deficiency anemia (IDA) (where the hemoglobin concentration falls below a pre-determined normal value). Anemia is defined as a suboptimal hemoglobin concentration (<110 g/L for children under five and pregnant women, <120 g/L for non-pregnant women and lactating women and <130 g/L for men). Half of the global anemia cases are directly attributed to iron deficiency, but anemia can also be caused by a deficiency of micronutrients other than iron, such as vitamin B12, folic acid, riboflavin and Vitamin A as well as other factors (diet, malaria, helminth infections, genetic factors, other infections, low birth weight and maternal nutrition).[6,8] The World Health Organization (WHO) estimates that up to 25% of men and 50% of women and children in developing countries are iron deficient. However, in developed countries, only 7 to 12% of children and women are iron deficient.[8]

ID also contributes to impaired physical work performance, developmental delay, cognitive impairment and adverse pregnancy outcomes. In pregnant women, IDA increases the risk of morbidity, mortality and low birth weight.[6] Increasingly, evidence shows that IDA in toddlers (12 to 18 months old) leads to irreversible developmental delays. Even when treated, the adverse effects from severe and prolonged IDA seem to persist. Such irreversible developmental delays (also seen with ID) are detrimental both to the individual's health and to the economic potential of the individual and their community.

Zinc Deficiency

While zinc deficiency (Zn-def) is becoming more recognized its incidence and prevalence have not yet been defined, mostly due to a lack of sensitive zinc status indicators and specific outcome or sypmtomatic characteristics of this malnutrition problem.[11] Just like VAD and IDA, ZN-def contributes to growth failure, increased susceptibility to infections and complications during childbirth.[6] ZN-def may pose a particular problem for those with HIV infection or malabsorption due to chronic illnesses.

Although the incidence of ZN-def is difficult to assess, its effects are undeniable. Evidence exists showing that zinc supplementation of at-risk populations leads to improved growth, reduces the morbidity and mortality of diarrheal diseases and lowers the incidence of respiratory tract pneumonia, two of the most common causes of death in children in developing countries. Not only can 'prophylactic' zinc supplementation reduce the incidence of diarrhea, it can reduce the severity, duration, mortality and morbidity of children already suffering from acute or chronic diarrhea.

Micronutrient Deficiencies: The concept of bioavailability

The long-term consequences of the Green Revolution phenomenon of the 1960s and 1970s are causes of the current global micronutrient deficiencies. The Green Revolution, initiated by some Latin American, Asian and African countries, was intended to eliminate world hunger by augmenting food supply. Crop yields were increased through the use of new cultivars, better irrigation and chemical fertilizers, pesticides and mechanization. Unfortunately, one of the outcomes of the Green Revolution was a decrease in the micronutrient content of a number of crops, probably a result of the heavy use of irrigation and chemical fertilizers which exhausted the soils.[12] This was detrimental because staple crops (rice, wheat and maize) represented the most commonly consumed food in developing countries.

Measuring the actual content of a nutrient (such as a micronutrient) in a diet or in a crop does not sufficiently assess adequacy. One must also consider the concept of nutrient bioavailability, specifically how much of a nutrient will actually be absorbed, transported to the body and used for physiological functions. Supplying adequate quantities of poorly bioavailable nutrients will not resolve the nutrient deficiency problem. The bioavailability of iron, for example, is a function of its chemical form and the presence of food components that either promote or inhibit its absorption. Important inhibitors of iron and zinc absorption are the phytates present in maize, wheat, sorghum and root crops, which drastically reduce the absorption of iron and zinc from a meal by binding them into a non-absorbable and insoluble form in the gastrointestinal tract. Polyphenols (e.g., tannins present in tea) and calcium are other known iron inhibitors although their clinical significance may be less than that of phytates.[13-14] On the other hand, the low consumption in developing countries of iron enhancers such as Vitamin C, which is present in citrus fruits and meat (the latter probably due to cost and religious beliefs and practices) decreases iron absorption and thus augments the problem.

Food Fortification: One solution to a problem

Pharmaceutical supplementation is one strategy that can be used to overcome or alleviate the prevalence of micronutrient deficiencies. This approach uses liquid or pill concentrates of micronutrients, which usually can provide high amounts of relatively highly bioavailable vitamins and minerals. However, despite many years of use, these supplements have had relatively little benefit globally, mostly because of poor compliance, coverage, commitment and distribution.[15] Although they work well in clinical trials, they are difficult to sustain without outside assistance because they are expensive, especially when the costs of manufacture and transport are considered.

A second potential solution is an agricultural-based approach to increase the micronutrient content or reduce the content of inhibitors of staple crops through selective plant breeding or genetic engineering.[16] For example, the bioavailability of iron and zinc from plant foods can be enhanced by reducing the amount of phytates and tannins and increasing the content of Vitamin C and sulfur-containing amino acids, such as methionine and cysteine, which may be responsible for promoting iron and zinc absorption.[12] With the aid of genetic engineering, human lactoferrin, the major iron binding whey protein in human milk, has been expressed in rice, and ferritin, an iron storage protein, recently has been introduced in rice plants.[17-18]

Consumer education is yet another possible strategy. It is possible to alleviate micronutrient problems by making the population more aware of techniques that can increase the bioavailability of micronutrients,. For example, iron and zinc bioavailability from plant foods can be improved through home processing techniques such as germination, fermentation and amylase treatment, which are known to be effective in reducing the levels of phytate in cereals and legumes. Avoiding tea and coffee or including citrus fruits, rich in Vitamin C, in the diet are other effective approaches.[19] Also, cooking foods in iron pots increases the intake of bioavailable iron in the foods, since iron is leached from the vessel during cooking.[20]

Although these pharmaceutical and educational approaches are important and must be pursued, they are far from being effective solutions to micronutrient malnutrition. In particular, some of the most healthful food strategies, including increasing the amount of dairy, fruits and vegetables in the diet, have economic costs that provide considerable barriers to widespread implementation among the most at-risk groups. Furthermore, families may opt not to change their practices, traditions and beliefs when it comes to food consumption, preparation, or both.

The agricultural-based approach, a sensible response to the malnutrition problem, requires years of further research, investments and massive education of not only the population but also crop breeders as well. This might be hindered by the anti-GMO (genetically modified foods) and anti-GEF (genetically engineered foods) sentiments that are currently globally spread. If this sentiment does not wane in the next years, it will be a barrier to the development, implementation and distribution of nutrient-dense staple crops.

A fourth approach to alleviating micronutrient deficiencies is to add micronutrients to foods or beverages in a process known as fortification. Fortification raises several issues that need to be addressed including, but not limited to, the form of the fortificant to be added, the prevention of undesirable sensory changes that the fortificant might bring and the choice of an appropriate food or beverage vehicle.

The type of fortificant to be added to the food will vary in cost, chemical form and bioavailability, which is closely linked to sensory changes. In general, the more bioavailable or absorbable a fortificant is, the more reactive and orlanoleptic problems (changes in color and flavor) they will cause in the food. For example, ferrous sulfate, a common iron fortificant with good bioavailability, has been known to cause fat oxidation and rancidity in cereal flours and lead to the development of unacceptable colors in salt and cocoa powders.[21] Consequently, other iron fortificants, such as elemental iron and ferric ammonium orthophosphate, which are less bioavailable and therefore less reactive, may need to be used for these products. Sodium iron ethylenediaminetetraacetic acid (NaFeEDTA) is another iron fortificant of similar bioavailability to ferrous sulfate, but it is six times more expensive.[21] Thus there is a need to choose fortificants with the highest potential absorption and the lowest potential to change the color and flavor of the food. Evaluating these issues is an ongoing area of research in many countries. We suggest that any country proposing to fortify a grain with iron, zinc, Vitamin A or folate conduct its own bioavailability and organoleptic testing prior to large-scale field trials.

The success of a fortification program depends, in large part, on the selection of the right food vehicle. The FAO has established well-defined requirements for potential food vehicles (e.g., the foods should be commonly consumed by the target populations, in adequate amounts but with low risk of excess consumption, be affordable, have stability during storage, etc.).[1,15] Salt has become the most common vehicle for iodine fortification. Sugar, dairy products (milk, milk powder, margarine) and oils have been used in Vitamin A fortification.[22] Cereal flours (maize, wheat) are the most common vehicle for iron fortification to reach the general population, followed by condiments and sauces.[23] Examples of vehicles for iron food fortification in the developing world include soy sauce (China), salt (India), fish sauce (Vietnam and Thailand), wheat flour (many countries), corn and wheat flour (Mexico), rice (Japan) and milk (Argentina and Chile).[24-25] Zinc fortified foods include wheat flour (sometimes co-fortified with iron, vitamin

B1, B2 and folic acid in India, Vietnam, China, Pakistan), wheat noodles (Thailand), wheat (Peru, Mexico), maize (Mexico), flour and milk (Chile).[26]

The advantage of using staple foods for fortification is that they do not require any changes in pre-existing beliefs, traditions or practices. There is no need to guide or educate consumers about improving their food selection or changing a particular behavior. By fortifying foods commonly consumed by the population, at-risk groups would acquire the micronutrients they need. Furthermore, since fortification uses the existing food production and distribution system, the addition of micronutrients, like iron or zinc, adds very little cost to the processed food.[16] For these reasons, fortification has been widely adopted in developed and industrialized countries. Fortifications of milk with vitamin D, of orange juice with calcium and of wheat flour with folic acid are examples of fortification strategies that are either mandated or have become important in the United States diet. Breakfast cereals are usually fortified with multiple micronutrients, including iron and zinc.

However, fortification of staple foods has not always been successful, due not only to poor bioavailability of the fortificant but also to poor distribution of the fortified food. For example, despite the common practice of adding iodine to salt, a commonly consumed condiment, IDD continues to be a problem in several developing countries, partly because some people, especially those living in rural areas, have no access to iodized salt. Consequently, they use naturally occurring salt (from seawater) instead. Industries responsible for iodinizing salt must be carefully monitored for compliance as well.

Fortifying foods with more than one micronutrient has the potential risk of nutrient interactions, such as iron-zinc interactions, and the large content of phytates and polyphenols in plant foods, which limit the quantity of iron and zinc that a person can absorb. Nonetheless, it is necessary to attempt multinutrient fortification since people who are deficient in one nutrient may well be deficient in others.[22]

Two Novel Approaches

In the past few years, two novel approaches to micronutrient supplementation have been developed that may be readily and widely adopted in the very near future. While similar to more widely-used pill supplements or grain fortificants, they represent somewhat unique methods of providing multiple micronutrients in an effective fashion. These approaches are: 1) the use of a single or multinutrient encapsulated packet (‘sprinkles’) and 2) the development of inexpensive multinutrient fortified beverages.

The use of microencapsulated nutrients, which can be opened and added directly (‘sprinkled’) onto a number of foods, is appealing because it allows for the high bioavailability of micronutrients without affecting other properties of the food to which it is added. The nutrients are encapsulated with an inert compound that protects the nutrient from oxidation and minimizes the organoleptic effects of the nutrient. Thus inexpensive and bioavailable forms of minerals, such as ferrous sulfate, can be used without concerns about storage and organoleptic properties, which enhance consumer acceptance and use. Although this method has potential problems with distribution similar to those of affecting other supplements, it is well suited toward school feeding programs and is easy and ready to use. Undoubtedly, the final cost to consumers and governments to develop a comprehensive program using available packets or new ones will be key to the initiative's implementation.

Recently, microencapsulated ferrous fumarate sprinkles coated with a lipid and containing Vitamin C have been tested on the iron status of infants and children.[27-28] One study found that this supplement significantly decreased the number of Ghanaian infants with iron deficiency and anemia after two months of treatment.[27] Newer forms of sprinkles have been developed; besides containing microencapsulated ferrous fumarate, they also contain zinc gluconate. While more research and clinical trials are needed to examine the effect of this multiple micronutrient supplement on the nutritional status of populations and on potential iron-zinc interactions, microencapsulated nutrients seem promising.

Another potentially effective option of supplementing the diets of children and adults with micronutrients is to use a beverage that is highly enriched with micronutrients. It is possible to develop multinutrient fortified food or beverages that are not only acceptable but also nutritionally stable and bioavailable as well. North Americans are used to such products since fruit juices often are fortified with calcium, Vitamin C and, more recently, zinc and vitamin E. However, few beverages are iron fortified due to its effect on the flavor of beverages and other micronutrients, such as riboflavin, are also difficult to add due their bitterness. Furthermore, it has proven difficult in the past to add a wide range of nutrients in forms that remain chemically stable during storage and are soluble in the final products. However, newer food processing techniques appear to have resolved many of these issues.

Currently, at least two micronutrient-fortified beverages have been developed that contain more than a dozen different micronutrients. They have been subject to testing in developing countries and have demonstrated effectiveness in substantially reducing micronutrient deficiencies. Preliminary data suggests that both beverages contain iron and zinc in highly bioavailable forms.[29-32] Iron- and zinc-fortified beverages are unique in providing many crucial micronutrients which may be especially lacking in developing countries.[29-31] A single serving of these products typically delivers about 50% of the daily requirement for zinc, up to 50% of the daily requirement for iodine, over 100% of the daily requirement for Vitamin C and 33% of the daily requirement of vitamin A, along with many other significant nutrients.[29,31] By making these drinks available in school feeding other public programs, in addition to selling them in stores, they can reach a vast number of individuals at risk for micronutrient deficiencies.

Although there is some concern that these drinks might increase the risk of tooth decay or obesity due to their sugar content, for populations at risk for obesity, lower calorie versions of such beverages could be made available.[31] Nevertheless, many children, especially in Africa and parts of Southeast Asia, suffer from an energy deficit and would benefit from the calories in these beverages.

Efficacy and acceptability studies of fortified beverages have been conducted in developing countries with promising results. Abrams and coworkers found better iron, riboflavin and folate status in 145 school children from Botswana who consumed a single daily serving of the beverage than in those who received an isocaloric non-fortified beverage.[31] The changes in anthropometric measurements (weight, mid-upper arm circumference, weight for age, body mass index) from the start of the study until the end, for a total of eight weeks, were better for the fortified beverage group than for the control group. Latham and coworkers found a larger increase in hemoglobin in the fortified group than in the nonfortified group.[29] Vitamin A status in the fortified group was better at the end of the study compared to the control, and, as in Abrams' study, they found higher incremental changes in weight, height and body mass index.[29] The beverage also significantly improved the nutritional status of Tanzanian women before and during pregnancy.[30] In that study daily consumption of the beverage for eight weeks reduced iron deficiency by 51% and iron deficiency anemia by 56%.

Therefore, the challenge at present is to identify the best and most cost-efficient methods for getting these new fortification methods (beverages and microencapsulated micronutrients) to consumers in developing countries. Because both methods represent a novel approach to healthy nutrition, their introduction must be accompanied by well-developed educational programs aimed at consumers and healthcare workers.

Conclusion

It is easy to understand why battles against diseases such as cancer and even against smoking-related disorders have been so difficult. Complex biology and social behavior must be dealt with in order to make progress. However, the global failure to combat micronutrient deficiency effectively is much more difficult to understand. Surely, no one wants to be nutrient-deprived.

Although the ultimate causes of micronutrient deficiencies lie in economic, environmental, cultural and social factors, nutrition scientists and food technologists have recently developed important new strategies to combat these problems. To date, successes have been limited in areas where economic development is slow, but it is likely that considerable progress can be made with the support of government agencies, non-governmental agencies and the private sector.

Very promising technologies and approaches include the widespread fortification of flour and rice grains with iron, zinc, folic acid and Vitamin A. More recent developments include encapsulated micronutrients and fortified beverages. The long-term effectiveness of any of these approaches, as well as their safety and cost-efficiency, must be demonstrated. However, it is likely that their use will rapidly increase in upcoming years, as will the need to further consider the role of food fortification and supplementation in global nutritional policy.

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