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Editorial

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Reconciling the Irreconcilable: Micronutrients in Clinical Nutrition and Public Health

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Editorial

Nutrition deficiencies, particularly micronutrient inadequacies are common worldwide. Because of poverty and food insecurity, macronutrient and micronutrient deficiency induce disorders that are most common in economically deprived, developing countries. There has been some reduction in global malnutrition over the past two decades, but a recent study has estimated that undernutrition remains a cause of 3.1 million deaths of children under 5, which is 45% of the total under 5 deaths in 2011 [1]. Micronutrient deficiencies are common (more than 2.5 billion individuals [2]),with estimates of over 100 million individuals being vitamin A deficient, over one billion with some degree of iron deficiency, chiefly in Africa and Asia, and over two billion people with vitamin D insufficiency (based on a cutoff of 50 nmol/L) [3]. However, underprivileged communities in affluent countries are not immune to these disorders, and in some cases, deficiencies can be widespread across certain populations (e.g., folate [4] and iodine [5]). Moreover, as recent studies have shown, even mild deficiencies, such as iodine inadequacy during pregnancy can lead to lower verbal IQ and reading comprehension, spelling and grammar in offspring [6,7].

Nevertheless, outcomes of alleviating micronutrient deficiencies, decreasing the disease burden, and the cost-effectiveness are exceptional in deficient communities [8,9]. Especially the poor living in developing countries would get the most benefit. In addition to enhancing the production of healthy food and assuring its wide availability and affordability to the low-income groups, the food industry should constantly develop healthful, nutritious foods using innovative technologies and market these products to consumers at affordable prices. At the same time, quality data and research are needed to address issues such as the development of right policies and procedures to alleviate mild micronutrient deficiencies, their effects on the human physiology and health, as well as their interactions with non-nutritional factors such as aging, socio-economic status, and medical drug interactions.

"Conflicts" of Evidence

We have recently celebrated the 100th anniversary of the "discovery" of vitamins. New meta-analyses indicate the benefits of multi-vitamins in reducing inflammation and cardiovascular risk factors [10] and the benefits of vitamin C supplementation [11] on improved endothelial function in subjects with cardio-metabolic disorders, but no demonstrable improvement was observed in healthy subjects. However, there is heterogeneity of results among studies.

In the Heart Protection Study, 20,536 adults in United Kingdom with coronary disease, other occlusive arterial disease, and/or diabetes did not show any benefits from "antioxidant" vitamin supplementation (600 mg vitamin E, 250 mg vitamin C, and 20 mg β-carotene daily) [12]. In addition to having study-design concerns, in many of these studies with neutral outcomes, vitamins and minerals were supplemented in populaces who are already sufficient with micronutrients. Thus, one would not have expected positive results from these studies. Nevertheless, based on such data, it is unfortunate that there have been recent calls for reductions in micronutrient supplementation in developed countries [13].

These variations in results may occur partially due to differences in nutritional status of the test subjects, and inadequately designed studies. In his 2003 EV McCollum Award Lecture, Robert Heaney divided nutritional issues between prevention of short-latency deficiency diseases such as beriberi, pellagra, rickets, and scurvy, versus long-latency, multifactorial disorders such as the chronic diseases increasing common globally; e.g., cancer, cardiovascular disease and diabetes [14]. The Nobel Prize-winning discoveries of the major vitamins and their ability to prevent or treat specifically caused diseases led to dramatic decline of those pathologies in the economically advanced counties. As a result, severe micro-nutritional deficiencies directly causing diseases are now found mainly in the developing economies.

A recent study in Cambodia found 50% of the women subjects in Phnom Penh and rural Cambodia were thiamine deficient (39% urban, 59% rural) [15]. In developed countries, thiamine deficiency and beriberi are rare on a population basis, but clinical deficiencies are reported worldwide [16]. Dealing with short-latency deficiency diseases is in principle relatively straightforward, the main difficulties usually being establishing the deficiencies at the population level. Recent, nationally representative studies in Indonesia and Malaysia reported vitamin D deficiency (using the cutoff of 50 nmol/L; 20 ng/mL) in over 60% of girls 7-12 years old [17-19], which had never been measured before. Fortification has proven to be an effective way to increase intakes of selected nutrients in both developed and developing countries [9], although sub-optimal data is often found in estimating population deficiencies and food intakes of potentially fortified foods.

Fortification

Key manifestations of severe under-nutrition caused by macronutrient malnutrition are marasmus (stunting, wasting, and underweight) and kwashiorkor (severe protein malnutrition).

However, numerous nutritional disorders exist secondary to different micronutrient insufficiency. Since it is cost-prohibitive to correct these individual deficiencies based on personal diagnosis, food fortification has become a practical and a cost-effective approach to solve this problem. The costs of the adding ingredients (vitamins and minerals) for fortification are estimated between 0.5% and 2.0% of the cost of a typical staple food [9].

Food fortification has a long history of effective implementation, starting with iodization of salt in the early 20th century. However to be effective, nutritional deficiencies need to be assessed, and food intake data of potentially fortifiable foods must be collected and analyzed, before implementing supplementation and food-fortification programs. It has been a common practice and convenient method to fortify one staple food. However, due to potentially wide variations in intake, the concept of fortifiable food energy (FFE) has been proposed to widen the potential range of fortified foods, leading to micronutrient intakes closer to ideal and to avoid excessive intakes [13].

In this approach, FFE is defined as the "total energy in the diet supplied by food-vehicles that manufactured by formal and centralized food industries and therefore amenable to be fortified in an efficient, cost-effective, and controllable way". This approach estimates high and low percentile intakes, rather than just per capita averages and acquiesce fortification levels that should be more appropriate. It does however, require time and expense to collect the necessary food intake data [20] and ideally, food composition data. In addition to the iodization of salt, this approach may not be useful for condiment fortification. However, the fortification of condiments in appropriate settings can be an effective approach [21]. The World Health Organization is facilitating the establishment of recommendations for condiment fortification that are expected in 2015.

Underlying causes for micronutrient deficiencies vary from economic reasons, such as access to food and food affordability, transportation, processing or cooking issues, or due to storage, cultural or eating habits. Understanding of these issues would facilitate the stakeholders to design cost effective solutions. The government and the department of health in a given country need to make nutrition and public health a priority through policies, and appropriate resource should be allocated. Micronutrient deficiencies associated morbidities, treatment costs, and loss of productivity can be overcome cost-effectively by proactively preventing these disorders.

Drug Interactions and Clinical Nutrition

At the clinical level, micronutrient status can be assessed or measured for an individual, and potentially appropriate intake levels can be supplied. However, for a population, all of the complicating factors must be taken into account. Average global population's ages are increasing, but micronutrient requirements in aging are often not well defined. It has been demonstrated that mitochondrial oxidative decay, a major contributor to aging and death, is accelerated by several common micronutrient decencies, including iron, zinc, copper, B6 and biotin among others [22]. Chronic low-grade inflammation, common in the elderly and those who live in unsanitary conditions, leads to less efficient absorption through hepcidin regulation [23]. Special fortified foods for the elderly have been proposed to provide estimated intake requirements for micronutrients, which may otherwise not be met by their reduced energy diets [24].

In industrialized countries, medical drug intakes are increasing, especially in aging populations, and some drug interactions with micronutrients are known, but few have been thoroughly investigated. For example, the regular intake of aspirin, commonly used for prevention of cardiovascular diseases, is associated with lower serum ferritin [23]. Drugs that use for treating hypertension and chronic heart failure, such as angiotensin-conversion enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) can lead to zinc depletion. Proton pump inhibitors (PPIs), widely used by the elderly, may inhibit absorption of vitamin C, vitamin B12, and iron, while metformin can also inhibit vitamin B12 absorption [25].

Diseases can lead to changes in micronutrient requirements, but generally, these are not well defined. As a recent review of micronutrients and cancer stated, "the optimal age for intervention, optimum dose in a given individual, and the duration needed to test nutritional agents for cardiovascular diseases or cancer prevention are largely unknown" [26]. Alterations in micronutrient status in diabetes mellitus have been well documented, and clinical trials have shown benefits for both single nutrients and combinations, but recommended intakes for prevention of prediabetes are not yet defined [27].

The Way Forward

Following the Heaney definitions, we may say that the short-latency deficiency diseases are relatively well understood and the chief issues are determining deficiencies in populations and taking effective steps to address the nutrient inadequacy. However, for long-latency deficiency diseases and complication of aging and drug interactions, we are still at an early stage of understanding, especially to the extent of translating the clinical experience to public health relevance. Many clinical trials have used standard doses of nutrients without taking into account the baseline nutrient status, and have found no benefit, which may be expected for doses given to mostly replete subjects or for inadequate dose levels insufficient to change the nutrient status. Prof. Heaney has recently proposed a series of rules for clinical trials and meta-analyses to help increase the clarity of the physiological responses [28]. However, these recommendations are difficult to follow without changing mindsets and current understanding. It will be especially important to incorporate the recommendation, "Co-nutrient status must be optimized in order to ensure that the test nutrient is the only nutrition related, limiting factor in the response," in designing RCTs.

Lindsay Allen recently stated that, "current guidelines for micronutrient interventions are patchy in that they omit important periods of life such as lactation; neglect some population groups such as schoolchildren, men and non-pregnant women, and the elderly" [29]. Added to this are gaps in understanding of micronutrient requirements in the prevention of chronic disease, in diseased states, drug interactions and individual heterogeneity of requirements and responses.

It is clear that there are often numerous biological pathways for various nutrients, and compensating mechanisms come into play. This is leading to a systems biology approach taking into account integrated nutrition and interactions. The endocrine, circulatory, digestive, nervous, and immune functions all rely on essential nutrients and interact with each other. Efforts are underway to collect high quality, high-dimensional genomic, proteomic, and/or metabolomics data suitable for nutrition analysis [30]. The Nutrigenomics Organization initiative (NuGO; http://www.nugo.org) has started development of a "collaborative, open data sharing, systems nutrition research program named ENOUGH (essential nutrients for optimal underpinning of growth and health) focused on individuals in undernourished populations". This also builds on the biomarkers project under the US NIH BOND (Biomarkers of Nutrition and Development [31], and EURRECA project to review micronutrient intake recommendations (http://www.eurreca.org/) [32], and the NuGO-led Micronutrient Genomics Project (MGP) [33].

Conclusion

The scaling up of sustainable resources for micronutrient status, food intake and composition data, making nutritious food available and affordable through public-private partnerships, educating and encouraging healthful lifestyles and the importance of balanced diet and good nutrition, would greatly facilitate overcoming micronutrient deficiencies. Progress has been made utilizing fortification, for example the increase since 1990 of the number of countries which are "iodine sufficient" from 6-8 to 112 using iodized salt [34]. Nevertheless, an estimated 2 billion individuals still have inadequate iodine intakes [35]. The cost-effective and practical micronutrient food-fortification programs should be designed to add micronutrients to common staple foods, such as flour or rice, as well as into appropriate condiments, depending on the cultural and food habits of individuals in a given country. Fortified packaged foods can also play an important role. Fortification has played a significant role in addressing micronutrient deficiencies in developed countries and increasingly in developing countries, requiring continuous monitoring and evaluation [36]. At the same time, careful research is needed at the clinical, molecular and genetic levels to identify optimal micronutrient intakes for populations and individuals.

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