Original Communication

Vitamins: Preparing for the Next 100 Years

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Abstract: The insights gained from the last 100 years of vitamin research and applications have contributed substantially to our fundamental understanding of biology and importantly to the promotion of human health. There is no reason to think that the next 100 years will be any less fruitful if we are committed to preparing for them, particularly by changing four critical nutrition paradigms. First, we must move beyond the concept of preventing vitamin deficiencies and inadequacies to establishing health and, further, to creating optimal physiological functions. Each essential vitamin possesses different concentration thresholds for its variety of effects and the required balance necessary to achieving each has yet to be fully defined. Second, we must apply the research approaches and methods of “-omics,” systems biology, and imaging technologies to define the dynamic role of vitamins and their broad array of genomic, molecular, biochemical, and functional interactions. Such work is necessary to understand the multiplicity of vitamin actions and ultimately apply them directly at the level of the individual. Third, we must revise the concept of evidence-based nutrition away from its current hierarchical system to recognize in a comprehensive and integrated way the attributes of each type of approach to research. To adhere to a single gold standard of the randomized clinical trial ignores both how we have moved forward so productively during the last 100 years and the vital information to be gained from basic research and other human studies; further, it acts to stifle innovation in both scientific and regulatory affairs. Fourth, we must understand that changes in the supply and distribution of food during the next century are likely to be at least as dramatic as those which have occurred over this last one. For example, inevitable environmental constraints will require more food protein be derived from plant than animal sources, a shift that will directly impact the dietary sources for vitamins. To meet the challenge of achieving global health in 2113 among a population of 9 billion people, effectively managing these four changes demands new and creative ways in which those in academia, government and non-government organizations, and industry must work together.

Key words: evidence-based nutrition, deficiency, optimal health, requirements, vitamins

Vitamins: From Preventing Deficiencies to Promoting Optimal Health

Important benefits to public health have been achieved from what we have first learned about vitamins and then applied that knowledge to individuals and their communities since Casimir Funk first described “vi-

tal amines” and “vitamines” in 1912 [1]. The insight gained from vitamin research has also contributed substantially to our fundamental understanding of biology and now suggests innovative new ways to continue the quest to promote human health and reduce our risk for common diseases. There is no reason to think that the next 100 years will be any less fruitful if we

are committed to preparing for them. However, this is no small challenge as it would be hubris to presume that our foods – and way we grow, process, transport, prepare, and cook them – will be the same as today in the next 50 or 100 years. Moving forward, we need to consider the ways in which we should define the role of vitamins beyond their original concept as dietary substances essential to preventing nutrient deficiencies.

Classical definitions viewed vitamins as substances essential in minute amounts for normal growth and activity of the body and obtained from plant and animal foods. Most vitamins were discovered because they were so closely associated with a corresponding deficiency disease, as was noted for conditions like beriberi, scurvy, rickets, and pellagra [2]. Thus, vitamins were first identified as useful to treat an established deficiency syndrome. Later, applications of vitamins for preventing an expected deficiency were found, including the fortification of milk with vitamin D and of refined flour with folic acid to reduce the incidence of rickets and neural tube birth defects, respectively. Similarly, administration of vitamin K to babies is now a standard approach to preventing hemorrhagic disease of the newborn. Today, we are beginning to appreciate the role of vitamins in the continuum of health from treating the very sick with total parenteral nutrition, to maintaining vitamin status sufficient to reduce the risk of deficiency in a population, to enhancing innate defenses against environmental and physiological stressors, and, ultimately, to promoting personalized optimal health and performance.

The dietary requirement for a vitamin is dependent on which criterion is selected to establish adequacy [3]. However, definitions of nutrient adequacy are neither fully clear nor consistent between countries or over time. For example, if the criterion selected for vitamin C is prevention of scurvy, then an adequate intake would be defined as 10 mg or less per day. However, if the criterion were the amount of vitamin C at which ascorbate is first excreted in the urine (as an approximation of saturation of body stores), then an adequate intake would be defined as a much higher value. Requirements for vitamin C today vary from 40 to 100 mg. Indeed, it is possible to have multiple recommended intakes, each corresponding to a different indicator or criterion of biochemical, cellular or physiological function. Considered in this manner, it can be appreciated that vitamins have multiple sites of action and, thus multiple thresholds for different functions. So, it is possible to have abnormal function in some parameters while other parameters for the same vitamin appear within normal range at lower doses. Indeed, the recognition of this dose-dependent

relationship between a vitamin and its many functions is one reason that recommended dietary allowances for most vitamins have changed over the last 60 years. Theoretically, a dose-response relationship might be developed between a vitamin and its associated capacity for reducing the risk of chronic diseases. For example, the dose of folic acid necessary to prevent megaloblastic anemia could represent one measure of adequacy, while a higher intake would be necessary to prevent neural tube birth defects, and higher intakes yet to reduce the risk of colorectal cancer, stroke or Alzheimer's disease. A similar dose hierarchy might be created for functional outcomes of folic acid like pyrimidine nucleotide biosynthesis, cervical dysplasia, homocysteine status, immune responsiveness, and cognitive performance. Importantly, simple relationships between a vitamin and its biochemical and cellular functions are rare.

Future research on vitamins needs to better appreciate the interrelationship between vitamins such that they are needed in the "right balance" for both efficacy and safety. Ready examples of this balance include the dependent interactions between folic acid, vitamins B2, B6, and B12, and choline in supporting one carbon metabolism [4] and between vitamins C and E as well as minerals like manganese, selenium and zinc and non-vitamins such as carotenoids and polyphenols in maintaining the antioxidant defense network [5]. Beyond the achieving the right balance between vitamins in determining their requirements for optimal health, is their further complex interplay with personal attributes like age, sex, and body composition as well as external factors like lifestyle (e.g., alcohol, physical activity, smoking) and exposure to environmental toxicants.

Emerging Approaches and Methods for Vitamin Research

Life expectancy has substantially increased over the last century due to reduced childhood mortality and improvements in sanitation, the advent of vaccinations, and improved medicine and nutrition. However, substantial benefits may still be achieved from optimizing nutrition to reduce the incidence of acute infectious diseases and chronic conditions like obesity, type 2 diabetes mellitus, cardiovascular disease, and cancer. This potential cannot be achieved without the application of recent advances in "omics," systems biology, and bioinformatics. These and other technologies can expand our understanding of the actions of vitamins

and allow us to apply them to patients in hospital and apparently healthy individuals at home as well as more broadly to population groups, particularly vulnerable communities. We should be able to elucidate the direct and indirect roles by which vitamins interact with genes to alter functional outcomes (genomics), induce changes in gene expression through methylation and other reactions (epigenomics), influence gene expression as ligands for nuclear receptors (transcriptomics), participate in the post-translational modification of proteins (proteomics), and change the profile of the vast array of circulating metabolites (metabolomics) to affect phenotype [6]. As these data are generated, they allow for the application of interactomics where the interactions between all these processes and the consequences of these interactions can be examined as a broad network (interactome). This presents a top-down approach to systems biology allowing an overall view of an organism, leading to hypotheses that can be tested by new experiments.

Imaging technologies – including computed tomography, functional magnetic resonance imaging, position emission tomography, and single photon emission computed tomography – now allow for whole body dynamic, non-invasive detection of body composition, gene regulation, and molecular tracers and probes. The application of these technologies, particularly in research on cognitive function, should provide a greater depth of information by following vitamin actions in location and time. As a part of this approach as well as in research using -omics techniques, there is a need to better incorporate observations that examine how vitamins can prevent or correct not just single points in biochemical pathways but the imbalances of overarching processes such as inflammatory stress, metabolic stress, oxidative stress, and psychological stress [6]. When exploring these clusters of biomarkers, it is also useful to do so in the context of homeostatic adaptability, where physiological systems are perturbed by some of these stresses and their attenuation by vitamin intervention followed [7].

We are still in the early stages of exploring the interactions between nutrition and the gut microbiome. However, it is clear that the nutritional value of food is partly influenced by the complex operation of the gut microbial community and that food in turn shapes the microbiota and, thus, the profile and function of its genes. This relationship is significant because intestinal microbiota have the capacity to synthesize vitamin K and several B vitamins, including B3 (niacin), B5 (pantothenic acid), B6 (pyridoxal phosphate), B12 (cobalamin), biotin, and tetrahydrofolate (Leblanc et al. 2012). Over 80 % of non-absorbed dietary vi-

tamin B12 is converted to bioactive corrinoids like *p*-cresol and methyladenine. The ability of the gut microbiota to produce folate and cobalamin could affect host DNA methylation patterns, but little is yet known about how these relationships between the host, host diet, and microbial community evolve and shape physiological phenotypes. However, it is interesting to note that vitamin A has the potential to modulate immune responses through direct interactions with immune cells as well as indirectly by modulating the composition of the microbiota (Cha et al. 2010). Research is needed to identify new host and microbial biomarkers and mediators of vitamin status to better establish the nutritional and health value of various foods. This approach would allow for a more rigorous definition of nutritional health and serve as a basis for preventive and therapeutic recommendations for vitamin consumption. Detailed investigation of the microbiome component of nutrition will help characterize an axis of our microbiome evolution that reflects our changing dietary habits and perhaps even uncover new aspects of the pathophysiology of ‘Western diseases’ to yield new microbiome-based strategies for disease prevention and treatment (Kau et al. 2013).

Evolving Paradigms for Evidence-Based Nutrition

We face an enormous challenge in trying to devise new ways to provide healthful food to a human population predicted to grow to 9 billion by 2050. Our success in developing new translational pipelines for defining the nutritional value of foods we consume now and those that we envision creating in the future depends on an evolution of the paradigm of evidence-based nutrition. This paradigm must now extend beyond the standard medical model using criteria more pertinent to treatment of the signs and symptoms of disease by drugs than to promoting health and wellness through our diet. Over the last decade, randomized clinical trials (RCTs) of vitamins and other nutrients for major disease entities have largely resulted in null or negative outcomes despite positive results from *in vitro*, animal model, and observational studies [12]. Because RCTs have traditionally been accepted as the “gold standard” for establishing cause-and-effect relationships, these studies have led to skepticism about the importance of supplemental vitamins alone or in combination with other nutrients in health and disease by clinicians, researchers, funding agencies, and the public. Nonetheless, the foundation of RCTs in evidence-

based medicine has now been wholly adopted in the creation of nutrition and science policy despite distinct differences between the evidence needed for testing of drugs versus that needed for the development of nutrient requirements and dietary guidance [13]. So, there is a need to better define the types of evidence necessary for developing dietary guidelines and recommending nutrient interventions, including those of vitamins, than that used for drug efficacy and safety. For example, unlike drugs, vitamins and other nutrients work in complex networks, are homeostatically controlled, and cannot be contrasted to a true placebo group (i.e., people not exposed to the intervention) because virtually everyone has been and continues to be exposed through their diet.

Although RCTs present one approach toward understanding the efficacy of vitamin interventions, the innate complexities of nutrient actions and interactions can only rarely be adequately addressed through a single research design. Further, action to define nutrient requirements or dietary recommendations to promote health should be taken at a level of confidence that is different from that needed in the evaluation of drug efficacy and safety in the treatment of disease [14, 15]. Moreover, in assessing the balance between the potential harm of making or not making a nutrient or dietary recommendation, appropriate educational strategies will be necessary to convey the varying levels of the strength of the evidence [16].

Requiring RCT-level evidence when this design is ill-suited or not available impedes the application of vitamin research to public health issues. Moreover, failing to act due to the absence of conclusive RCTs jeopardizes the potential for achieving substantial benefits with little risk and low cost. Interestingly, the L.E.A.D. Framework (for Locate Evidence, Evaluate Evidence, Assemble Evidence, Inform Decisions) to inform decision-making uses a broader base than an exclusive reliance on the requirement for RCTs to address the urgent need to bridge the evidence gap regarding obesity prevention [17]. It is noteworthy that the L.E.A.D. Framework was designed as an innovative way to consider and research complex questions that need to be answered soon. This approach to research specifically addresses deviations from the status quo with respect to methods considered to be the gold standard but which are responsibly designed to inform policy. Advancing evidence-based nutrition from its current version to one based upon more relevant and realistic criteria will depend upon research approaches that include RCTs but go beyond them. Achieving this goal will require new models of coop-

erative rather than adversarial interactions between industry, government, and academia.

The Future of Food Production and Vitamin Needs

Changes in the supply and distribution of food during the next century will be driven by several major factors, including the adverse impact of climate change, the declining availability of clean water, and the growth of the human population. Feeding a world populated by over 9 billion people will require us to double our food production on a planet where virgin land available for new farming is limited and concerns exist about overfishing of the oceans. More than another “green revolution” with new hybrid seeds and chemical fertilizers will be required to meet the demand for more food. Food, farm, and water technologists are exploring not only novel ways to produce more food but to examine less common and new kinds of food to eat. Part of this exploration must include considerations for the content and/or changed requirements of micronutrients like vitamins associated with these new foods.

Entomophagy, the consumption of insects and arachnids as food, is neither new nor novel as it is common to several cultures in developing regions of Africa, Asia, and elsewhere. It is estimated that 1400 species are edible to man. Entomophagy as a source of protein is cited as an ecologically sound concept providing greater efficiency, lower resource use, and environmental sustainability compared to traditional livestock. However, little attention has been directed to insect consumption as a source of micronutrients and how these foods might need to be fortified with vitamins to ensure adequate intakes.

Algae are also consumed in several cultures, particularly in Asia where it has long been a staple. There are about 145 species of brown, green and red seaweed currently used as food and, as they are grown in the ocean, generally obviate the need for land and fresh water. Like insects, algae can also be formulated into a variety of types of food products and fortified to ensure healthful intakes of vitamins.

A potentially novel source of food is that of artificial or *in vitro* meat, sometimes called shmeat, cultured from stem cells biopsied from livestock. While still in its early development, this approach to protein food could also be ecologically sound with less energy and water consumed and less greenhouse gases produced than associated with raising cattle, hogs, and sheep.

Based on techniques being tested to build tissue and organ structures for the purpose of regenerative medicine, experiments are currently underway to employ three-dimensional bioprinting to create meat products. This process builds the meat with minute droplets of cultured cells “printed” layer by layer via a controlled jet nozzle. Again, the micronutrient content of meat products that might be produced in this manner has not been considered.

Genetically engineered foods are not uncommon today and this method may find even more application in the future. To date, this approach is more frequently employed to increase agricultural productivity than to address the need for nutrients like vitamins. Importantly, achieving the benefits of both traditional and novel foods in the future will not be possible without employing and integrating the full capabilities of modern agriculture and aquaculture, food and pharmaceutical companies, and retail industries that distribute and market foods and food ingredients to consumers.

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