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Editorial

Personalized Medicine: The Contribution of Micronutrients

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In the Merriam-Webster dictionary micronutrients are defined as compounds that are '*essential in minute amounts to the growth and health of an animal*'. Over the past130 years, remarkable researchhas defined the'*minute*' micronutrient intake range to avoid deficiency or toxicity in healthy human and mice [1,2]. This knowledge helps to improve and prevent diseases associated with micronutrient deficiencies worldwide. For example,vitamin A supplementation decreases night blindness in pregnant women with vitamin A deficiency andreduces mortality among their newborn infants [3,4]. In China, supplementation with multiple vitamins and trace elements has helped to reduce alarming numbers of esophageal and gastric cancer casesin deprived populations [5]. In contrast, in nutrient sufficient industrial countries, micronutrient supplementation hasexhibited disappointing resultsin large populations. The results of meta-analyses of multiple studies suggests that micronutrient supplementation, especially with lipid soluble vitamins, can increase mortality by up to 15% [6]. A consistent improvement in metabolic conditions has been predominantly observedin specific patient groups supplemented with vitamins[7]. Nonetheless, recent studies shake upthe dogma that vitamin A supplementation improves immune responsesin deficient populations [8,9]. Vitamin A effects are dependent on specific pathogens and occur in a sex-specific fashion, *e.g.*vaccination outcome can be either improved ordeleterious among boys and girls supplemented with vitamin A compared to placebo groups[10].Thus, any vitamin supplementation, particularly vitamin A, should be used cautiously. In spite of the various outcomesobserved in widespread clinical studies, these findingsare conceptually in agreement with current molecular research dissecting micronutrient functions.

Micronutrients, such as trace elements and vitamins, are critical components of regulatory circuitswithin the body [11-13].They can act as primary messengerhormones, secondary messengers, and activators/inhibitors of transcriptional machinery for gene regulation. In addition, micronutrients cancontrol membrane transporters and membrane potential. They also act as key components of enzymatic catalytic centersand oxygen carriers within hemoglobin. Thus, minimal elevation of '*minute amounts*' can result in aberrant signaling causing toxicity or pathogenesis. We increasingly understand that achievement of healthy micronutrient homeostasis depends on many factors:

Gender: Vitamins and trace elements are needed at different levels in males and females. In females, the demand in micronutrient and micronutrient functions depends on the estrous cycle (oestrous cycle), pregnancy, and menopause [14,15]. In males, micronutrient demand depends on testosterone levels [16].

Macronutrients: Macronutrients, drugs, alcohol, and environmental pollutants interfere with micronutrient absorption [2]. Both macronutrient catabolism and cell proliferation lead to an increasing demand of micronutrient requirements. Emerging studieshaveshown that macronutrients canalso regulate conversion of vitamin precursors into bioactivemetabolites [17]. For example, a high-fat diet induces retinoic acid generation from vitamin A and increases retinoic acid-dependent gene regulation. This increase in retinoic acid promotes development of deleterious visceral obesity [15]. Counterintuitive to the understanding of obesity, as a macronutrient disease of energy-overload, micronutrientsplay a causative role in the development of obesity. In our studies, ablation of retinoic acid production prevents obesity in animals fed a high fat-diet [15,18].

Micronutrients: Micronutrients can influence each other's absorption in competitive or synergistic fashions. Similarly, micronutrient-regulated pathways can act interact in a competitive, additive, or synergistic manner. For example, vitamin A metabolizing enzymes and retinoic acid receptors contain zinc (Zn). In the absence of Zn,patients experience a functional vitamin A deficiency,despite adequate blood and tissue vitamin A levels [2].

Microbiome: Micronutrients selectively support growth of specific intestinal microorganisms, that determine micronutrient availability for a host organism and influence many metabolic, inflammatory, and cognitive disorders [19].

Epigenome (Pathologies and aging) **:** Chronic inflammation and metabolic dysregulation accompany aging and a number of pathologies including obesity, diabetes, and cancers.Inevitably, micronutrient demand is altered in the course of pathogenesis and influences the outcome of diseases [2]. Since micronutrients can both promote or inhibit metabolic and inflammatory pathways [13,20], it is critical to elucidate which micronutrient composition is most beneficial to specific diseases and what amount of these micronutrients isneeded to improve patients' recoveries. Endocrine status of patients is another variable that greatly influences micronutrient demand and regulates production of bioactive vitamin metabolites.

Genome variations: Differences in susceptibility to metabolic disorders, cancer, and infectious disease have been observed in patients from different ethnic backgrounds. These responses have

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been attributed in part to polymorphism in transcription factors regulated by bioactive vitamin metabolites or genes responsible for the conversion of micronutrients to their bioactive form [21,22]. However, whether polymorphism also influences bioavailability, storage, and transport of micronutrientsrequires further investigations.

These aforementionedfactorshighlight only some of the major processes influencing micronutrient concentrations in the body. Our citations were not aimed at reviewing thecomprehensive field of micronutrients in this Editorial, but intended to provide a few representative examples of studiesand reviews supporting these concepts. Given the complexity of factors influencing micronutrient demands, it seemsimplausible that over a countermultivitamin supplement can provide optimal micronutrient levels in any group of patients. Rather, the future of preventive medicine and therapies lays in supplementationof specific micronutrients followingpersonalized assessments. The goals of nutrition and food sciencestoday liesindeveloping efficient micronutrient detection methods for fast and cost-effective assessments of micronutrient levels, their absorption, storage, and conversion to bioactive metabolites in the body. The elucidation of micronutrient functions in specific model environments will enable the creation of databases for computerized assessment of micronutrient needs of individual patients. In the same way that the global positioning system changed the world of transportation and communication, our Journal will serve as a platform for the development of a global nutrition optimization system that may change the face of healthcare and preventive medicine.

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