Personalized Nutrition: Optimizing Essential Nutrient Status through Testing and Supplementation

Introduction

Since Casimir Funk first described "vital amines" in 1912, we have seen major improvements in public health through sizable reductions of then commonplace deficiencies [1]. Yet over 100 years later deficiencies in a multitude of macro- and micronutrients (e.g. Vitamin D, E, Omega-3 fatty acids) remain highly prevalent in the general United States (US) population [2]. These nutritional deficiencies have been found to raise the risk of a wide array of health outcomes including the leading causes of death (i.e. cardiovascular diseases, malignant neoplasms, diabetes, and cerebrovascular diseases) [3-10]. Therefore, addressing them is of vital importance to continue to build on the progress we have made thus far, but we also need to move beyond just preventing deficiencies toward the optimization of health and performance for each individual. This dossier will lay out the current state of nutrient intakes in the US, its consequences for human health, and how moving to objective measurements of nutrient status coupled with customized dietary supplement protocols will enable individuals to not just avoid deficiencies but optimize intake for maximal fitness and well-being.

Importance for Health, Fitness, and Well-being

Each essential nutrient has been shown to play a vital role in a wide-array of functions in the human body [11]. Therefore, it is not surprising that deficiency can have severe effects on human health. Poor diet has been found to be the leading risk factor for premature death and

disability in the US, posing a greater risk to health than smoking, hypertension, and obesity [12]. This is based on the fact that nearly half of all cardiometabolic deaths (i.e. heart disease, stroke, and diabetes), over 700,000 annually, are associated with a suboptimal diet (e.g. low fruit, vegetable, and Omega-3 rich seafood intake) [13].

Health Benefits of Key Nutrients

Long-chain ω-3 polyunsaturated fatty acids (ω3-PUFAs), in particular, eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA) provide a wide range of health benefits. Higher levels of ω3-PUFAs are associated with lower total mortality, especially death from coronary heart disease [14]. Nearly all U.S. adults (95.7%) have ω3-PUFAs levels below concentrations associated with cardiovascular protection [15].

Magnesium is an essential mineral necessary for more than 300 chemical reactions in the human body [16]. Unfortunately, the majority of Americans are not consuming even an adequate amount of magnesium [17]. Low magnesium is linked to an increase risk in coronary heart disease, heart failure, and sudden cardiac death [18, 19]. Higher magnesium intake is associated with a reduced risk of bone fractures, type-2 diabetes, stroke, and death from all causes [20-23].

Vitamin D is involved in a multitude of biological functions, including calcium homeostasis, metabolism, and immune function [16]. Deficiency is prevalent (41.6%) among U.S. adults [24]. Poor Vitamin D status (i.e. concentrations too low or high) is associated with an increased risk of headaches [25], liver disease [26], diabetes [27], multiple sclerosis [28], cognitive decline [29, 30], rheumatoid arthritis [31], cancer [32-40], hypertension [41], heart disease [42, 43], bone fracture [44], and death from all causes [45].

Further details of the main functions and effects of deficiency of the nutrients most commonly low in American diets are shown in Table 1.

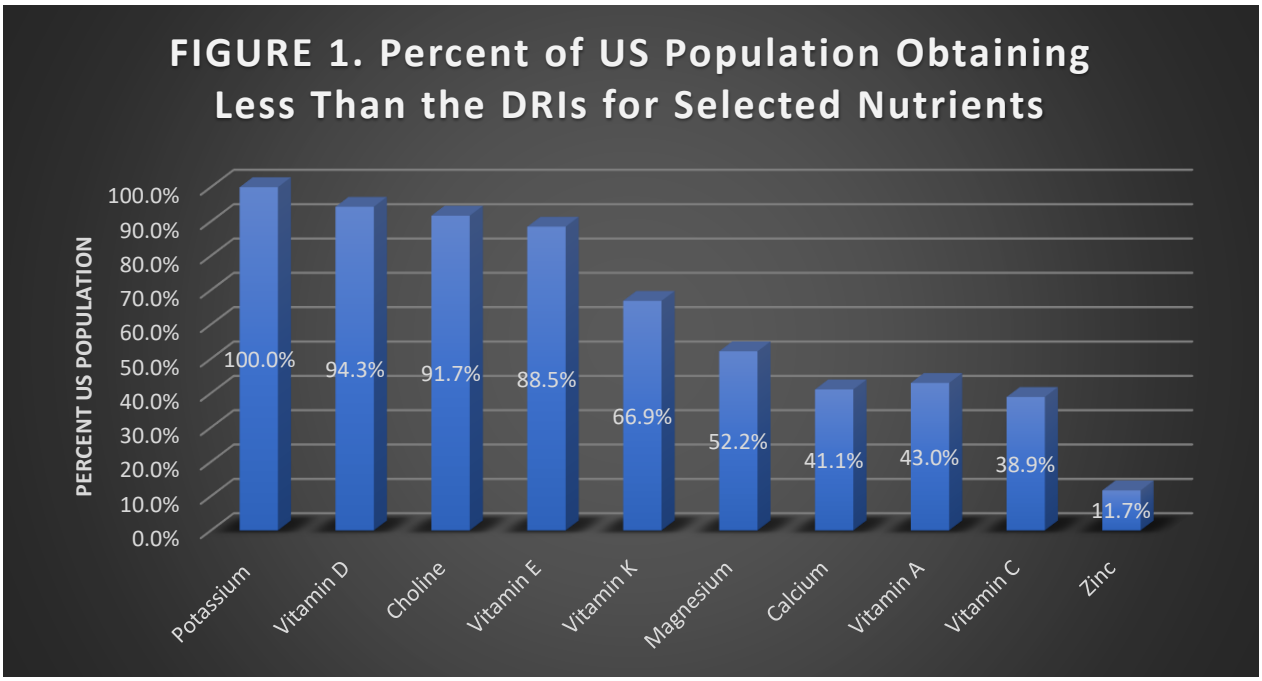
TABLE 1.

Essential Nutrient	Main Functions	Effects of Deficiency
Omega-3 Fatty Acids	muscle activity, blood clotting, digestion, fertility, and cell division and growth	fatigue, poor memory, dry skin, heart problems, mood swings or depression, and poor circulation
Zinc	growth, brain function, and immune system	slow growth, impotence, hair loss, diarrhea, eye and skin sores, loss of appetite, impaired wound healing, and lower alertness levels
Magnesium	protein synthesis, muscle function, blood glucose control, blood pressure regulation, energy production, synthesis of DNA, RNA, and glutathione, nerve impulse conduction, and normal heart rhythm	loss of appetite, nausea, vomiting, fatigue, weakness, numbness, tingling, muscle contractions and cramps, seizures, personality changes, abnormal heart rhythms, and coronary spasms
Choline	metabolism, cell membranes, memory, mood, muscle control, modulating gene expression, cell membrane signaling, and early brain development	muscle damage, liver damage, and nonalcoholic fatty liver disease
Potassium	build proteins, break down and use carbohydrates, build muscle, maintain normal body growth, Control the electrical activity of the heart, and control the acid-base balance	weak muscles, abnormal heart rhythms, and a rise in blood pressure
Vitamin A	vision, immune system, reproduction, proper function of the heart, lungs and kidneys	blindness

Vitamin C	antioxidant, immune system	fatigue, joint pain, poor wound healing, anemia, and depression
Vitamin D	bone health, nerve and immune function	rickets, bone pain, and muscle weakness
Vitamin E	antioxidant, immune system	peripheral neuropathy, ataxia, skeletal myopathy, retinopathy, and impaired immune response
Vitamin K	bone health and blood clotting	osteoporosis, bleeding, and hemorrhage
Calcium	bone health, nerve and muscle function, and proper release of hormones and enzymes	numbness and tingling in the fingers, convulsions, and abnormal heart rhythms

Food and Generic Supplementation Is Not Enough

The National Health and Nutrition Examination Survey (NHANES) is a yearly survey by the National Center for Health Statistics of the health and nutrition status of a nationally-representative sample of Americans [10]. The most recent reported NHANES intake data (2007-2010, n=16,444) found that the majority of Americans do not meet the Dietary Reference Intakes (DRIs) set by the Institute of Medicine (IOM) for numerous essential nutrients (e.g. vitamins and minerals) [17] (See Figure 1).



The majority of American use multivitamin multimineral supplements (MVMM). Users of MVMM supplements have superior intake of a number of essential nutrients compared to diet alone, but still often fail to meet recommended intake levels, while also occasionally exceeding the tolerable upper limit (UL), increasing the risk of toxicity [17, 46].

Objective Measurements of Nutrient Status

In last twenty years, we have seen a paradigm shift across numerous industries toward data-driven management of decision making processes. We are just beginning to see this occur in healthcare where evidence-based and precision medicine are being applied to leverage data to optimize down to the individual patient. We are in dire need of a similar shift to occur within nutrition to close widespread gaps in nutrition and move towards, meaning to optimize nutrient intakes towards individual needs.

The status of essential nutrients in the body is typically estimated by using measurements of nutrient intake as a proxy. This is problematic for a multitude of reasons. 1) The tools used to assess nutrient intake (e.g. food frequency questionnaires (FFQ) and food diaries) require large amounts of effort by individuals in the collection of data [47, 48]. 2) The data collected on dietary intake may not accurately reflect what was consumed due to recall error, day-to-day variations in intake, and biased food inclusion data [49-53]. 3) The nutrient content of a particular food varies considerably due to differences in cultivation and preparation methods [54, 55]. 4) Different forms of a specific nutrient vary in their bioavailability [56-61]. 5) There exists a large inter-individual and intra-individual variability in the absorption, excretion and demand of nutrients [62-64].

Direct measurement of nutrient status via validated biomarkers circumvents the problems associated with accurately measuring nutrient intake, but its use has been limited due to issues pertaining to cost, inconvenience, invasiveness, and the body fluid volumes required for proper analysis.

Using Dietary Supplements to Optimize Status

Once an accurate nutrient status has been determined an effective and safe intervention must then be applied to correct for deficient and suboptimal nutrient levels. The majority of Americans fall short of achieving even adequate nutrient intake through diet alone [17, 46]. Conversely, dietary supplements are well suited for this need.

The U.S. Food and Drug Administration (FDA) defines a dietary supplement as,

"a product intended for ingestion that contains a "dietary ingredient" intended to add further nutritional value to (supplement) the diet. A "dietary ingredient" may be one, or any combination, of the following substances:

- *a vitamin*
- *a mineral*
- *an herb or other botanical*
- *an amino acid*
- *a dietary substance for use by people to supplement the diet by increasing the total dietary intake*
- *a concentrate, metabolite, constituent, or extract*

Dietary supplements may be found in many forms such as tablets, capsules, softgels, gelcaps, liquids, or powders. Some dietary supplements can help ensure that you get an adequate dietary intake of essential nutrients; others may help you reduce your risk of disease." [65].

It's been demonstrated in a multitude of studies that dietary supplements are an effective and safe means of optimizing nutrient status in various populations [66-71]. These improvements in essential nutrient status translate into tangible health benefits for users. For example, supplementation with **ω3-PUFAs** has been shown to reduce triglyceride levels, a biomarker for heart disease, by 20% to 50%. Additionally, supplementation with ω3-PUFAs is beneficial for eye health [72-75], dysmenorrhea [76], weight loss [77], stress [78], blood pressure [79, 80], cognitive function [81-87], mental health [88, 89], liver function [90], inflammation [91, 92], muscle strength [93], muscle mass [94], heart health [95], exercise recovery [96], and anaerobic endurance [97]. **Magnesium** supplementation has been found to convey a wide range of health benefits for users. These include lower blood pressure [98], improved blood glucose levels [99],

improved insulin sensitivity [100-102], stronger bones [103, 104], superior physical performance [105], better sleep [106-108] and reduction of asthmatic symptoms [109-111]. Supplementation with **Vitamin D** results in improved immune function [112, 113], birthweight [114], liver function [115], blood glucose [116, 117], insulin sensitivity [116-118], blood pressure [119, 120], muscle strength & mass [121, 122], cognitive function [123, 124], mood [125-127], sleep [128] injury prevention [129], fat loss [130], and testosterone levels in men [131]. Finally, the benefits of supplementation with **Zinc** have been demonstrated for sleep quality [132], consequences of obesity [133], mood [134], infections [135-137], liver health [138] and acne [139].

Safety of Dietary Supplements

Reasonable concerns have been raised as to the long-term safety of dietary supplement use after a few high-profile studies found that supplementation with certain nutrients resulted in an increase in disease risk (e.g. cancer, stroke) [140, 141]. One important common flaw in the design of these studies has been the lack of an objective measurement of nutrient status. Whereas, trials that have assessed baseline nutrient status have found reductions in death from cancer and all causes with micronutrient supplementation [142-144]. Many micronutrients follow a U-curve for optimal status relative to disease risk, with low and high levels both resulting in compromised physiological functioning [145]. This underscores the importance of measuring nutrient status and its inclusion in all randomized clinical trials (RCTs) evaluating dietary supplementation and health outcomes [145-147].

Moving Beyond Generic Supplementation

To this point a review by Cochrane, that included 56 randomized trials with a total of 95,286 participants, found that Vitamin D supplement use was associated with only a 2% reduction in risk of all-cause mortality [148]. In comparison, a review of 14 studies with a combined total of 62,548 participants found that optimal Vitamin D status was associated with a 31% lower risk of death by any cause when compared to deficient status [149]. This difference between generic supplementation and status has also been seen with Omega-3 fatty acids. A review of 10 studies involving 77,917 participants found that Omega-3 fatty acid supplementation had no significant association with fatal or nonfatal coronary heart disease or any major vascular events [150]. In comparison, risk for cardiovascular mortality was found to be 30% lower with an omega-3 index >8%, in comparison with an omega-3 index of <4% in a meta-analysis of 10 cohort studies [151].

Case Study

To test the concept of optimizing nutrient status through blood-based biomarker guided dietary supplement protocols a 10-week trial was conducted with 48 participants. The seven tested (and accordingly supplemented) biomarkers were alpha-tocopherol, cholecalciferol, copper, magnesium, selenium, zinc and combined EPA and DHA. Participants were retested after four weeks and a final measurment was done six weeks later. Their personalized dietary supplement protocols were adjusted accordingly. 32 participants participated in all three tests (Figure 2). All of them showed at their first testing at minimum one deficit out of the seven tested biomarkers. The median number of deficits was two while 15 participants showed three or more deficits.

After 10 weeks, the median number of deficits declined clearly to one. 7 participants showed no deficit and only four participants were left in the class of three or more deficits. Improvements were seen across all nutrient biomarkers tested.

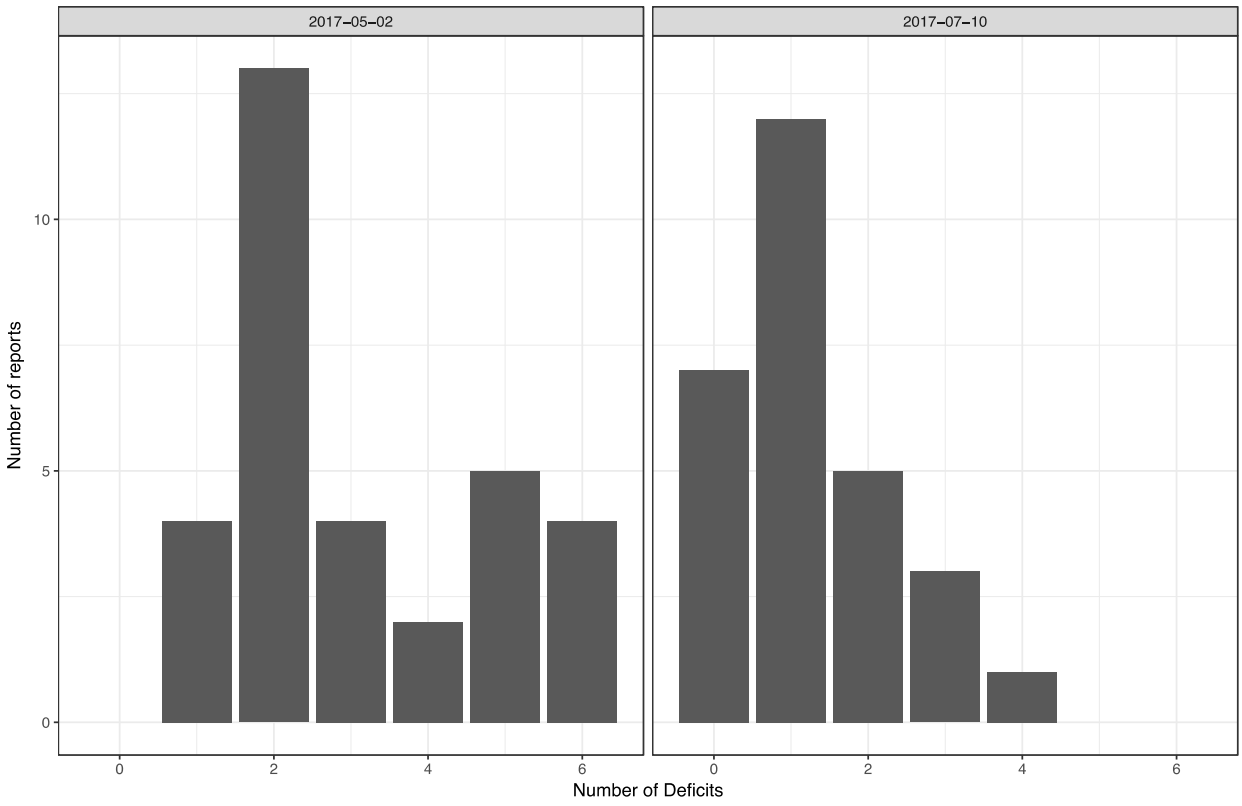


Figure 2: Histogram of the distribution of deficits among 32 participants treated over 10 weeks with the blood-based biomarker guided dietary supplement protocol. The left part shows the distribution at the beginning of the trial, i.e. before supplementation. The right part shows the distribution after 10 weeks.

Conclusion

Suboptimal intake of essential nutrients is widespread and has a profound impact on human health and performance. Current methods for measuring nutrient status and dietary supplement use fail to meet the needs of individuals. We have demonstrated that nutrient status

can be optimized through the use of personalized dietary supplement protocols (PDSP) that are based on regular testing of blood-based biomarkers. We plan to build on these findings and investigate how PDSPs compare to other current methods for determining dietary supplement recommendations (e.g. survey, broad-category, generic).

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