Supplementing Dietary Nutrients

A Guide for Healthcare Professionals

SECOND EDITION

Defining Optimal Nutrition • Nutrients as Genomic & Epigenetic Signals • Protein Supplementation
Fatty Acid Supplements • Vitamin Sources & Forms • Mineral Sources & Forms
Natural vs. Synthetic Vitamins • Whole Food vs. Isolates • Choosing a Probiotic
Botanical & Phytonutrient Basics • Fundamentals of Dietary Supplement Regulations
Deciphering Supplement Labels • Prenatal Supplementation • And Much More....

THE STANDARD
ROAD MAP SERIES

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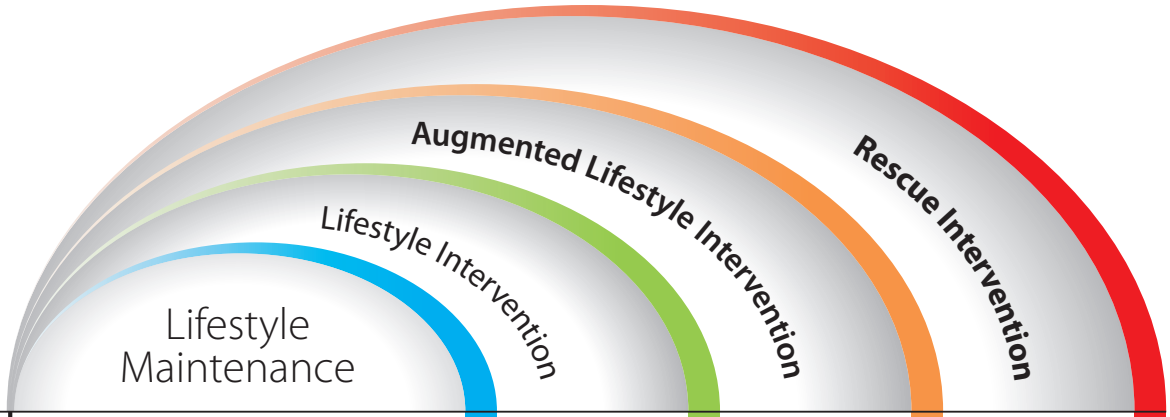
POINT INSTITUTE

Table of Contents



Vitamin D & Bones	Sunlight: Work and Play	Sun Therapy/ Diet	Vitamin D Supplement	Osteoporosis Drugs
Antioxidant Defense	Wholesome, Diverse Diet	↑ Fruits & Veggies	Supplement Vitamins C and E/ Quercetin etc.	N/A
Back Health	Normal Physical Activity	Exercise and Flex Training	Chiropractic/ Physical Therapy	Surgery/Pain Medications
Joint Health	Physical Activity/Hydration	Weight Loss/ Flexibility	Glucosamine/ Chondroitin Sulfate	Drugs, Knee Replacement
Cancer Prevention	Wholesome, Diverse Diet	↑ Fruits & Veggies (Cruciferous)	Supplement Sulforophane or I3C	Antineoplastic Drugs
Detoxification	Wholesome Living	Avoidance/ Organic Focus	Supplement Agents that ↑Detoxification	Drugs to Combat Toxin Symptoms

Table 1: The Prevention to Intervention Hierarchy. This table shows examples of the relationship between each stage of the Prevention to Intervention Hierarchy. Notice that as we move from left to right along the continuum, the intention is to add signals, not replace them. For instance, the key to cancer prevention from a dietary standpoint is to eat a wholesome and diverse diet with many signals that support immune function and build the metabolic reserve that protects DNA from damage. Some individuals with higher risk or family history may choose to be more specific about increasing their "dose" of certain fruits and vegetables to maximize the dietary signals that help prevent cancer. An example of augmented lifestyle therapy is the use of concentrated phytonutrient supplements derived from these plants (e.g., sulforophane from broccoli) that have been tested for their ability to reduce cancer. In every case, a wholesome and diverse diet sets the foundation for each point along the continuum. Note that rescue interventions rarely trigger the same sorts of mechanisms as those designed to be triggered by lifestyle signals.

a dietary pattern that emphasizes ingredients containing bone-building micronutrients and may choose to perform more weight-bearing physical activities. In another example, a person with low serum vitamin D levels may choose to expose themselves to more sunlight. In each case, there is a reliance upon the body's capacity to build or rebuild metabolic reserve, but there is a greater focus on risk prevention based on a person's specific vulnerability.

Weight loss is one of the most common reasons people use lifestyle intervention, and one of the most common endpoints used in lifestyle intervention trials. Studies like the Diabetes Prevention Program (DPP) have shown that, when implemented correctly, lifestyle intervention strategies can be remarkably successful — often more so than pharmaceutical therapies.[6]

Augmented Lifestyle Intervention

Having discovered many of the specific mechanism(s) linking our lifestyle decisions to our health, we are now capable of designing therapies to target those mechanisms. These therapies are the heart of functional medicine—modalities like nutritional and nutraceutical therapy, osteopathic or chiropractic manipulation, detoxification protocols and many more. For instance, recognizing the role of beneficial microbes found in our foods and environment, we may consider the therapeutic role of adding foods containing live bacterial cultures, or we may augment the diet with probiotic supplements for a more potent therapeutic outcome. Likewise, there are a wide array of nutrients known to increase insulin sensitivity, modulate lipid metabolism, decrease protein glycation and reduce inflammatory signaling. These "*signals*" can be used to augment and reinforce the benefits already coming from the implementation of other lifestyle interventions to achieve better (and quicker) patient outcomes. For the most part, this Road map discusses the supplementation of dietary nutrients outside of their traditional matrix (i.e., unfortified foods), which is one of the most important categories of augmented lifestyle therapy. The relationship between supplemented nutrients and food-derived nutrients is discussed further throughout this Road map.

Rescue Intervention

Rescue interventions, now commonplace in our modern medical system, mostly involve drugs and surgery. We recognize that these interventions are often necessary tools to rescue the patient and to prevent organ damage, major debility or death. In the acute setting, rescue interventions prevent thousands of individuals from dying from cardiovascular events each day. However, when the same paradigm of rescue intervention is adopted for the prevention and treatment of chronic diseases for which these therapies were not intended, a person's metabolic reserve and physiological resilience are rarely enhanced. In fact, these buffering systems are often depleted. Obvious examples of this are drug-induced nutrient depletion or nutrient malabsorption following bariatric surgery. Since the pharmaceutical burden weighs heavily on most patients diagnosed with chronic conditions, wise clinicians who intend to use lifestyle therapies as the core of their intervention strategy must understand how to manage patients who have been treated with, or are currently on, these rescue therapies.

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Building Metabolic Reserve Through Diet and Supplementation

Since the purpose of this Road map is to guide healthcare providers and their patients in the appropriate use of supplemental nutrients, we provide only a limited discussion of healthy dietary principles. Nonetheless, it is our view that one of the most important overall principles to build and sustain human health is to increase and diversify the number of good signals coming from the diet, but not in a way that causes the person to exceed their appropriate amount of energy (calories) or that increases the amount of bad dietary signals (noise). We call this principle: increasing the dietary signal-to-noise ratio. This ensures that the genomic and epigenetic signals (discussed further below) that maintain our health and build our metabolic reserve will never be more than a meal or two away. Thus, the key is to recommend a dietary pattern that includes diversity, seasonality, color (naturally, not artificially) and freshness.

In our view, the diet that meets these principles best and has been tested repeatedly as an intervention strategy amongst Western subjects consuming a (mostly) Western dietary pattern is the Mediterranean diet (MedDiet).[1] This diet, or a modified version of the MedDiet, can be implemented by most patients in most communities regardless of their socioeconomic status. Other dietary patterns with similar principles include the DASH, Nordic, Okinawan, and MIND diets.[2-6]

A Healthy Dietary Pattern (e.g., Mediterranean Diet)

- Fresh and cooked vegetables
- Generous use of herbs and spices
- Legumes/plant proteins (such as beans, lentils) and whole grains (such as bulgur, rice, quinoa and wheat berries)
- Fresh fruit at each meal
- Lean meats such as fish, chicken and lamb
- Moderate dairy products, mostly as yogurt & cheeses
- Monounsaturated fats and omega-3 fatty acids in the form of nuts, olive oil and fatty fish
- Moderate intake of red wine or phytonutrient-rich juices (pomegranate, berries etc.)
- Reduced consumption of red meat, processed meats, refined grains and sweet foods
- Avoidance of pre-packaged foods

Diversity: Good for You and Your Gut Microbiome

While certain essential nutrients have been identified for over a century, there are many food-related compounds that have only recently been identified as having health-related benefits. As such, many important nutrients may not be specifically listed on food labels and have no recommended dietary allowance. In fact, many of the health-promoting compounds in plants are just being discovered. This is why dietary diversity is so important; it allows for the intake of a wider variety of phytonutrients that are likely to positively influence human metabolism. These compounds might have a direct effect after absorption into the blood, but they often influence human health by first modulating the function of bacteria living in the human gastrointestinal tract. Ironically, while scientists still argue about how to define a healthy gut microbiome for any given individual, the feature upon which they most agree is diversity. A healthy gut microbiome is highly diverse in both the type of organisms and their metabolic activities; and one of the greatest influences on gut microbiome diversity is the number of different plant species a person consumes on a regular basis.[7-9] This can be accomplished with traditional vegetable consumption, but is greatly enhanced by the use of herbs and spices, known for their rich content of bioactive phytochemicals.[10,11] For a discussion of supplementing herbal, botanical or phytonutrient ingredients, see pages 271 - 275.

The Functions and Signaling Capacity of Essential Nutrients

One way of describing cellular metabolic functions would simply be: a complex rearranging of nutrients. This is well understood when it comes to macronutrients. Proteins and amino acids are rearranged as new structural components, cellular receptors, hormone signals, and a vast array of enzymes that accomplish nearly every important metabolic task in the body. Absorbed carbohydrates function as important energy sources and are also critical for modification of proteins (glycosylation); unabsorbed carbohydrates are also very important to help with bowel transit time and as fermenting substrates for commensal bacteria in the GI tract. Finally, fats have an array of functions as long-term energy stores, components of cell membranes and as precursors to important signaling molecules such as prostaglandins and pro-resolving mediators. In general, macronutrients function as building blocks for cell structures, as sources of energy and as signaling molecules.

Micronutrients also have a wide range of biological activities. We often think of vitamins mostly in their role as precursors to enzyme cofactors (e.g., NAD, FAD, etc.) but they also function as pre-hormones (e.g., vitamins A and D), antioxidants (e.g., vitamins C and E) and methyl donors (e.g., 5-MTHF, choline). Minerals are also necessary cofactors for important enzymatic reactions (e.g., Mn-SOD, Mg-ATP, etc.), but they also function as portions of important cellular proteins (e.g., iodine-thyroid hormone, iron-hemoglobin) and as signaling molecules in the cell (e.g., calcium). All of these functions, and more, are described amply in any good nutrition textbook and are also summarized briefly in the *"Essential Nutrient Function"* section in each of our nutrient monographs starting on page 79. It is important to note that the *"adequate"* intake of each nutrient may be different for each of these functions. In other words, in order to optimize all the potential biological functions of any given nutrient, the overall intake may need to be greater than that which is needed for the most basic functions of that nutrient.

Genomic and Epigenetic Signaling of Nutrients

For most cells, a change in function often includes more than simply ligand-binding of a receptor or activation of an enzyme, it involves turning specific genes on or off within the nucleus. The effect of nutrients on gene expression is known generally as **nutrigenomics**†. Within this overall term are several other terms that define how a nutrient signal is converted into a change in cellular function or phenotype. The change in messenger RNA transcripts (upregulation and downregulation) is called *transciptomics*; the change in total protein expression is called *proteomics*; and the resultant change in the metabolites produced, *metabolomics*. Much of the current understanding of nutrient function within specific cells comes from the molecular biology techniques that define nutrigenomics (see Figure 4).

In general, nutrigenomic changes can be subtle; however, increasing or decreasing gene expression by just 25% in a single gene may still greatly influence the metabolic function of the entire cell. There are many nutrients known to change the expression of not just one gene but hundreds of genes, sometimes altering their expression two-to-three-fold (or more); these can obviously have a tremendous impact on cellular function and clinical outcomes. Perhaps the greatest example of this within the essential nutrients is vitamin D. In essence, vitamin D acts as a genomic regulator through its interaction with the vitamin D receptor, a transcription factor that influences the expression of hundreds of different genes (see Figure 5).[12]

The largest category of nutrigenomic signaling agents are not strictly considered *"essential nutrients"*— they are the thousands of phytonutrients derived from fruits, vegetables and spices. These bioactive compounds have often been noted as being poorly absorbed after consumption, but they often function at very low doses because genomic signals often require low serum concentrations, or they influence human biology by modulating the gut microbiota (see discussion of bioavailability issues of phytochemicals on page 276). In fact, *"omics"* — based preclinical research is now routine for the investigation of hopeful bioactive therapeutics from plants.[13,14]

† Nutrigenomics is sometimes also used to describe all nutrient-gene interactions, including those that fall under the category of nutrigenetics, epigenetics and other "omics" related to nutrient intake.

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Optimal Nutrition: How Is It Defined — Can It Be Achieved?

As with many other health-related phenomena, nutritional needs have been historically explored and defined within the context of deficiency-related diseases. Because of this history, *adequate nutrition was considered to exist where known symptoms of nutritional deficiencies* ***appeared*** *to be absent*. In other words, nutrient needs were defined as a means to avoid nutrient-related dysfunction, rather than to optimize metabolic function. Consequently, the discovery that specific foods were able to treat or prevent specific nutrient-related "disease" conditions (e.g., scurvy, rickets, etc.) helped scientists isolate most of the compounds we define as essential nutrients today. Even so, with all of the knowledge gained about essential nutrients and nutrient-deficiency diseases, it is still difficult to answer one of the most clinically-relevant nutrition questions: *Is the nutrient status of a specific patient adequate to maintain their optimal health and, if not, what changes to their nutrient intake should be recommended to improve their health?*

Undoubtedly, our understanding of nutrition has advanced well beyond the notion of *minimal* quantities to prevent deficiency-related diseases, though this is still often how nutrition intake is framed within the clinical setting. It is now recognized that varying degrees of nutritional insufficiencies exist in individuals, which prevents them from achieving optimal physiological function, while lacking overt signs of nutritional deficiency. However, distinguishing the many signs and symptoms of a nutrient insufficiency often requires significant clinical experience. From a nutrient-deficiency-disease standpoint, these insufficiencies may be deemed "subclinical," but individually and collectively they create a major physiological burden and are a significant contributor to diminishing an individual's metabolic reserve and their resilience against both acute and chronic diseases.

Therefore, it is important to define several different terms that are often used to describe the degree to which an individual's relationship to a nutrient is "optimal." First, however, we must distinguish between terms used to describe a person's nutrient *status* and a person's nutrient *intake*. For instance, a person may consume a nutrient well above its recommended dietary allowance, an intake that many would consider to be optimal. However, other signs and symptoms, or laboratory evaluation, may show a less than optimal nutrient status. Consequently, it is the relative difference between nutrient intake and nutrient status that creates many of the nuances in defining optimal nutrition for a given individual.

Defining Nutrient Intake vs. Status

For the most part, optimal nutrient intake is mostly defined by how much is consumed (usually calculated using food databases, food frequency questionnaires, dietary recall and a diary of supplement use). A person's calculated intake of a particular nutrient can then be compared to the dietary recommended intake for that nutrient. In this case, their calculated level of intake is compared to databases generated by asking similar questions to "healthy" subjects to determine the average intake needs among large populations.

Because most individual and population-based nutrient recommendations are based upon intake levels, it is often assumed that if a person's calculated intake of a nutrient is above the RDA, they must have an adequate (or even optimal) nutrient status. This assumption is often incorrect. Therefore, clinicians should distinguish between definitions of nutrient intake vs. nutrient status for which we provide these categories along with analogous financial terms to help understand the differences. It is important to note that a person's intake/status may be different for each nutrient and insufficiency in one nutrient can lead to clinical symptoms even when most other nutrients are consumed at adequate amounts.

Intake Deficiency: The intake of the nutrient is below the threshold required to maintain minimal physiological functions required by that nutrient in most subjects. Individuals with long-term intake deficiencies will exhibit traditional signs and symptoms associated with nutrient status deficiency. These levels are generally (although not always) similar across genders, ethnicities and ages. In financial terms, this would be bankruptcy.

Intake Insufficiency: A person's nutrient intake is above the level that results in a frank deficiency-related disease outcome, but the level is still inadequate to maintain optimal nutrient status and to adequately facilitate all the necessary functions performed by the nutrient. In financial terms, this is being behind on payments and having a low credit score.

Functional Insufficiency: In this situation, a person's nutrient intake is functionally disconnected from their nutrient status. In other words, a person's nutrient intake is below their *current* physiological need (even if the intake amount is deemed sufficient by population estimates), a situation usually caused by one of the conditions below.

- Poor absorption caused by:
  - Poor food matrix
  - Poor eating habits (inadequate chewing, etc.)
  - Low stomach acid, enzyme production or other factors needed for absorption
  - Bowel transit time (usually too fast)
- Improper metabolism of nutrient to active or transport forms
- Increased elimination/detoxification of nutrient
- Drug- or toxin-induced depletion
- Increased physiological need (e.g., athletic need)
- Genetic defect or polymorphism altering need (nutrigenetics — see page 24)
- Deficiency in a different but physiologically related nutrient
- Alterations in gut microbiota (species or metabolism)
- Overconsumption of some food or nutrient, reducing function or absorption
- Obesity
- Stress- or sickness-induced depletion

When one or more of these conditions is combined with intermittent low intake, clinical symptoms of deficiency are not uncommon. Financially speaking, their income looks good on paper, but they are spending more than they take in (or someone is embezzling from their account).

Adequate Nutrient Intake: A person is regularly consuming the nutrient at a level that prevents clinical or subclinical symptoms of nutrient insufficiency and compensates for any functional nutrient needs listed above. These levels are physiologically *adequate* under the current metabolic needs of the subject, though they may be inadequate for optimal function under stressful metabolic conditions or insufficient to build metabolic reserve for future physiological challenges. In financial terms, they are living paycheck to paycheck and have no official debt—but they are unable to plan a big vacation and they hope that the furnace doesn't give out.

Optimal Status/Intake: This defines the ideal situation where nutrient intake is adequate to satisfy the individual's current physiological needs and to overcome chronic or transient causes of functional insufficiency; it promotes metabolic, cellular and organ reserve. In financial terms, all the bills are paid and there are enough savings to plan a vacation without detrimentally impacting your retirement plans.

Therapeutic Intake: There are times when the desired intake of certain nutrients will be higher than that needed to optimize its status; where the nutrient is being used for targeted therapy. These nutrients are essentially being used for their pharmacological, rather than physiological, potential (e.g., high-dose niacin for lipid management or high-dose folate for homocysteine reduction). Sometimes referred to as orthomolecular medicine, this sort of therapeutic use of nutrients is not designed to manage nutrient deficiencies per se, but to act as a strong signal intended for a physiological response. Often, these doses exceed the Institute of Medicine's (IOM) safe upper limit and should be monitored for safety when recommended.† Financially, this is like receiving a large donation to help with a special purpose, like setting up a college fund or adding onto a home.

Excessive Intake: This occurs when intake of any nutrient interferes with optimal physiology or results in toxicity. While many nutrients have a "Safe Upper Limit," defined by the IOM, these levels are often set to be very conservative (below the safe therapeutic levels used in many clinical trials) and often do not consider the use of these nutrients as therapeutic agents (i.e., orthomolecular medicine). Although rare, clinicians should be aware that patients who self-diagnose and self-medicate with dietary supplements may be getting an excessive intake of some nutrients. Financially speaking this is like winning the lottery without having financial restraint, leading to excessive or dangerous life decisions.

† Please note that the Institute of Medicine (IOM) changed its name to the National Academy of Medicine and joined the National Academy of Sciences and National Academy of Engineering in 2015. Throughout this Road map we refer to this group as the Institute of Medicine (IOM), as most of the publications used to support our text were published by the IOM before this name change.

Products sold as "whole-food," which clearly are not:
Though we will discuss the labeling requirements for dietary supplements in more detail elsewhere (see page 302), it is important to know that the regulations require that each vitamin and mineral with a Daily Value requirement be listed with the compound from which it is derived in the Supplement Facts panel of the label. For instance, vitamin B_{12} must also include (usually in parentheses) the compound from which the claim is derived; methylcobalamin, cyanocobalamin or some other form of B_{12}. This makes it easy to spot a vitamin or provitamin source on any properly labeled product. However, some manufacturers and marketers simply do not know the difference or, believe the public won't know the difference, between a *"synthetic"* ingredient and a *"naturally-derived"* ingredient. In many cases, they use alternative names or slightly unique forms to disguise this fact.

As an example, review the Supplement Facts Box shown below; this was used for a product once widely marketed as a *"whole-foods"* multivitamin. While this formula may very well be a good multivitamin product, it is in no way delivering these vitamins and minerals as whole foods or whole-food derivatives. In fact, of all the vitamins and minerals listed, only a handful (beta-carotene, vitamin E, biotin, iodine) might be deemed *"naturally sourced"*; while all the others have been modified or synthesized from other starting materials. Notice that while additional food ingredients have been added to the multivitamin, none of these ingredients are listed in the parenthesis for the vitamin claims. In other words, these food ingredients are not intended to be viewed as the source for any of the vitamin or mineral claims. Another confusing issue for consumers and unknowledgeable manufacturers and marketers is the idea that using so-called activated forms or combined forms, in order to avoid the most obvious synthetic compound names, makes the product appear more natural. In this product, the use of mineral or vitamin ascorbates is used to obscure the fact that these compounds are merely salts (or mixtures) derived from commercial ascorbic acid—with calcium, magnesium, palmitic acid, niacin. For this product, *"whole-food"* is simply a marketing gimmick to sell a fairly common multivitamin.

Supplement Facts

Serving Size: 8 Tablets — Servings Per Container: 30

Amount Per Serving		%DV
Vitamin A (from natural beta carotene)	5,000 IU	100%
Vitamin C (as Calcium, Magnesium, Niacinamide Ascorbates and Ascorbyl Palmitate)	500 mg	833%
Vitamin D-3 (as cholecalciferol)	5,000 IU	1,250%
Vitamin E (natural, as d-alpha tocopheryl plus mixed tocopherols)	400 IU	1,333%
Thiamine (as Thiamine Pyrophosphate)	3 mg	200%
Riboflavin (as Riboflavin-5-Phosphate)	3.4mg	200%
Niacin/Niacinamide (as Niacinamide Ascorbate)	40 mg	200%
Vitamin B-6 (as Pyridoxal-5-Phosphate)	4 mg	200%
Folate (as L-methylfolate, Metafolin®)	400 mcg	100%
Vitamin B-12 (as methylcobalamin)	100 mcg	1,667%
Biotin	900 mcg	300%
Pantothenic Acid (as d Calcium Pantothenate)	30 mg	300%
Calcium (as Calcium Ascorbate, Citrate/Malate Complex)	250 mg	25%
Iodine (from Kelp)	200 mcg	133%
Magnesium (as Magnesium Ascorbate/ Amino Acid Chelate Complex)	500 mg	125%
Zinc (as Zinc Amino Acid Chelate)	15 mg	100%
Selenium (as Amino Acid Chelate Complex)	200 mcg	286%
Copper (as Copper Amino Acid Chelate)	50 mcg	3%
Manganese (as Manganese Amino Acid Chelate)	2 mg	100%
Chromium (as Amino Acid Chelate)	200 mcg	167%
Molybdenum (as Amino Acid Chelate)	100 mcg	133%
Potassium (as Potassium Krebs† and Amino Acid Chelate Complex)	99 mg	2%
Lutein (natural)	6 mg	*
Lycopene (natural)	6 mg	*
Zeaxanthin	1 mg	*
Other Minerals, Nutrients and Trace Elements		
Inositol	100 mg	*
Trace Elements (from Sea Vegetation)	approx. 100 mcg	*
Strontium (from 0.5 mg strontium carbonate)	297 mcg	*
Silica	100 mg	*
Choline (from 150 mg Choline Citrate/Bitartrate)	60 mg	*
PABA (para-aminobenzoic acid)	50 mg	*
Boron (as Amino Acid Chelate Complex)	1.5 mg	*
Vanadium (as Amino Acid Chelate)	50 mcg	*
Amino Acids and Enzymes		
L-Cysteine/N-Acetyl L-Cysteine	150 mg	*
Betaine (from 150 mg Betaine HCl)	114 mg	*
Bromelain (2,000 GDU/g)	50 mg	*
Glutamic Acid (from 25 mg Glutamic Acid HCl)	20 mg	*
L-Methionine	12.5 mg	*
Bioflavonoids and Proanthocyanidins		
Rose Hips	100 mg	*
Lemon Bioflavonoids	100 mg	*
Red Wine Proanthocyanidins/Pine Bark Extract	50 mg	*
Hesperidin	35 mg	*
Rutin	25 mg	*
Vegetables Fruits and Herbs		
Proprietary Blend: Kale (leaf), Spinach (leaf), Carrot (root), Radish (root), Celery (leaf and stalk), Apricot (fruit), Blackberry (fruit), Cranberry (fruit), Grape (fruit) and Pineapple (fruit).	700 mg	*
Blueberry (fruit)	100 mg	*
Garlic (bulb, Pure Gar®, odorless)	100 mg	*
Broccoli (entire plant)	100 mg	*
Cauliflower (entire plant)	100 mg	*
Spirulina	100 mg	*
Chlorella (broken cell wall)	100 mg	*
Green Papaya Extract (fruit)	100 mg	*
Green Tea Extract (leaf)	50 mg	*
Sprouted Barley Juice (entire plant)	50 mg	*
Wheat Grass Juice (entire plant)	50 mg	*
Beet Extract (root)	50 mg	*
Apple Pectin (fruit)	50 mg	*

*Daily Value not established.

There are a host of products with similar designs (adding fruit and vegetable powders to a standard multivitamin blend) masquerading as natural or *"whole-food."* Because the term *"whole-food"* is not defined from a regulatory standpoint, the marketers of these products have done a great disservice to the nutrient supplement world and added much confusion to patients and clinicians, intentionally or not. Thankfully, these products should be easy to spot due to the mandatory disclosure of ingredient sources within the supplement facts box; something that was not true prior to 1997. If a dietary supplement product does not list the parent compound for each vitamin and mineral, it is misbranded and should not be considered a reliable product.

Products made with mostly non-food yeast extracts or wheat germ:
Concentrating and stabilizing vitamins and minerals from a food material, predominantly fruits and vegetables, is expensive and difficult. Recent technologies have increased the availability of some food-derived vitamins and minerals, though most still provide only low doses of most essential nutrients at a premium price. For this reason, many products that attempt to use only unmodified vitamins source these from extracts of yeast fermentation, often labeled as *Saccharomyces cerevisiae* or just *S. cerevisiae*. Wheat germ is also sometimes used, though it is less popular with today's gluten-free focus. These products will sometimes have a few other, non-yeast or wheat germ, ingredients included to supply vitamins that are not high enough in the yeast or wheat germ extracts. However, if they haven't been spiked with undeclared vitamins, these products will also be limited in the doses of most vitamins, but especially low in their mineral content.

While these types of products are designed to avoid ingredients they claim are *"unnatural,"* the notion that a concentration of fermented yeast grown in a factory represents a natural food source is a bit of a stretch, and since these products deliver a limited amount of nutrients, their clinical utility is also limited. If these products are labeled correctly, clinicians and patients can decide if they are helpful in their quest for sufficient nutrient intake.

Products made with ingredients spiked with undeclared synthetic vitamins:
Marketers of *"whole-food"* nutrients quickly realized vitamins and minerals are difficult to concentrate and deliver from legitimate whole-food sources. So, when using non-yeast foods such as fruits and vegetables, it is difficult to deliver even measurable amounts of vitamins or minerals, the levels

of which are well below the US RDA. Consequently, a number of deceptive methods have been used to sell products higher in vitamins and (some) minerals, while claiming the ingredients to be food-derived or natural. This is accomplished by various techniques, usually described in marketing literature and websites as a patented or unique process, sometimes referred to as some form of *"culturing"* or *"fermentation."* Essentially what these marketers, or their raw material suppliers, are doing is adding large amounts of synthetic vitamins to the process (fermentation vessel of yeast or foods) at some point prior to *"extraction"* and then claiming the measured vitamin content is from the natural source. These products typically avoid making source claims within the Supplement Facts box, but vaguely describe patented or proprietary processed sources in a notation below or outside the box. They use a loophole in the GMP regulations that does not require the labeling of every processing aid used to create a raw ingredient (if it is not an allergen). By intentionally spiking the raw materials before the manufacturing of the finished product (tablet or capsule), these companies can falsely (and knowingly) mislead the consumer to believe the vitamin and mineral claims on their *"whole-food"* product is derived from food ingredients.

While these products may deliver the vitamin content they claim, these deceptive and fraudulent practices lead to confusion about nutrient supplementation and falsely imply that high doses of naturally-sourced vitamins and minerals can be delivered in capsules for a reasonable price. By doing so, they falsely exaggerate the differences between whole-food sourced vitamins and those they deem harmful (synthetic isolates), while at the same time using these same ingredients to *"fortify"* their product by deceptively hiding behind their proprietary process.

Are Mineral Supplements Natural?

The *"natural"* vs. *"synthetic"* debate which characterizes the marketing of different vitamin forms also extends to the sources of mineral compounds. However, unlike vitamin molecules which are synthesized by some biological organisms, minerals cannot be synthesized per se; they simply move between the soil, water, air, plants and animals. Nonetheless, mineral compounds used for food fortification or dietary supplementation are almost always modified (and different) than those encountered in nature; from eating plants or animals; and drinking ground water. The low concentrations of dissolved minerals in water are primarily in their ionic form (e.g., Ca^{2+}), while food forms of minerals (especially those from plants) are mostly bound within complexes of proteins or other organic compounds.

On the other hand, minerals used for food fortification and supplementation are typically purified mineral salts or organic complexes; mostly created by reacting concentrated mineral sources with other ingredients. For instance, calcium carbonate is a naturally-occurring salt found in limestone, chalk, coral and seashells which can be used directly in supplements; however, it is often dissolved and combined with an organic acid (e.g., ascorbic acid, citric acid) and precipitated to make a new calcium salt (e.g., calcium ascorbate, calcium citrate). These mineral salts can differ in many important characteristics—percent of mineral content, solubility, pH, bioavailability—differences that may affect their clinical effectiveness. Complicating matters further, dietary guideline recommendations for mineral intake do not distinguish the source of the mineral, nor are they standardized for the differing bioavailability of various mineral compounds. Furthermore, unscrupulous ingredient suppliers often misrepresent some mineral blends as new *"reacted"* compounds when they are merely blended powders.

Unreacted blends and true reacted minerals

When commercial sources of supplemental mineral compounds are created by reacting two ingredients, such as magnesium oxide and ascorbic acid, a new compound is formed upon precipitation: magnesium ascorbate. Made correctly, the finished materials should have little unreacted magnesium oxide or ascorbic acid present. However, it is not uncommon for ingredient manufacturers to simply blend these two ingredients as dry powders, while still labeling the mixture (incorrectly) as magnesium ascorbate. The problem is the unreacted blend, a much cheaper final product, does not have the properties of the truly reacted new compound (e.g., pH, solubility, bioavailability, etc.). Unfortunately, since regulators are more concerned about the accuracy of the elemental mineral claim, little focus in product testing is placed on distinguishing the precise makeup of the mineral compound.

Why does this matter? As many of the monographs will describe, the bioavailability of different mineral compounds often differ from one another. A particular example is the vast difference between the bioavailability of equivalent levels of magnesium found as magnesium oxide and magnesium ascorbate. Magnesium ascorbate has a lower mineral content, but a truly reacted compound allows for much higher magnesium bioavailability compared to magnesium oxide. However, when the high mineral content of magnesium oxide is diluted by being blended with, rather than reacting with, ascorbic acid, this poorly absorbed form is made worse by merely diluting its mineral content without increasing its bioavailability. Companies with knowledgeable quality control laboratory personnel and appropriate methods and procedures should be able to distinguish a mineral blend from a truly reacted compound. In many cases, purchasing

Table 3: Amino Acid Profile of Commercially Available Protein Supplements and Foods

	Rice Protein	Pea Protein	Soy Protein	Whey Protein	Egg White Protein	Whole eggs, scrambled	Breast Milk	Crickets, whole[15]	Bone Broth, beef	Collagen[16], Fortigel® AA Profile
Typical PRO % of ingredient	80%	80%	90%	80%	80%	10%	1.03%		98%	
Typical AA Profile Essential AA (as % of protein)										
Tryptophan	0.8	1	5.3	1.92	N/A	1.39	1.66	2.53	0.2	N/A
Threonine	3.8	3.8	3.8	8.86	4.34	4.42	4.50	3.09	2.0	2.20/1.8
Isoleucine	5.03	4.7	4.6	6.21	4.53	5.32	5.48	3.36	1.6	1.68/1.4
Leucine	9.4	8.2	8.1	12.42	7.53	8.61	9.31	6.62	3.6	3.87/2.7
Lysine	3.6	7.1	5.7	9.62	5.87	7.05	6.66	5.29	3.6	4.36/3.6
Methionine	2.8	1.1	1.5	2.61	4.90	2.97	2.05	2.29	1.0	0.90/0.9
Phenylalanine	6.8	5.5	6.2	3.4	5.31	5.35	4.50	3.37	2.3	2.38/2.1
Valine	5.4	5	4.7	5.81	6.45	6.76	6.17	4.63	2.6	3.47/2.4
Histidine	2.3	2.5	2.4	1.85	2.18	2.45	2.25	2.52	1.0	1.18/1.0
Non-Essential AA										
Alanine	5.01	4.3	4.1	4.57	7.5	5.66	3.52	6.23	8.0	
Arginine	8.7	8.7	7.4	2.42	5.25	6.23	4.21	4.14	7.0	8.78/8.6
Aspartic Acid	9.06	11.5	11.6	12.76	10.46	10.34	8.03	8.25	5.7	7.79/7.3
Cysteine	1.5	1	1.1	0.76	N/A	2.05	1.86	1.14	0.1	6.21/5.8
Glutamic Acid	17.2	16.7	19.6	19.48	13.12	13.78	16.46	10.60	10.5	0.00/N/A
Glycine	4.3	4	3.6	2.06	3.28	3.35	2.54	4.03	19.0	10.45/10.2
Proline	3.8	4.3	4.7	7.76	3.53	4.53	8.03	5.09	11.0	21.99/22.2
Serine	5.4	5.1	5.3	5.91	6.40	7.42	4.21	3.80	3.0	10.07/12.7
Tyrosine	5.1	3.8	5.3	3.32	N/A	4.02	5.19	4.23	1.0	3.57/3.2
Hydroxyproline	N/A	N/A	N/A	0.1	N/A	N/A	N/A	N/A	8.0	1.13/0.8

Supplementing Macronutrients: Carbohydrates

Carbohydrates are a major class of macronutrients which are further subdivided into monosaccharides, disaccharides, polysaccharides and starch. In foods and supplements, all other organic compounds other than fats and proteins (e.g., polyol sugars, fiber, plant cellulose, etc.) are measured as carbohydrates. From an energy perspective, carbohydrates contain four calories per gram.

US RDA	Men (Adults)	Women (Adults)
Carbohydrates	130 grams (520 calories)	130 grams (520 calories)
"Added sugars"	(Up to 25% of total calorie intake)	

The recommended intake levels (USRDA) for carbohydrates and "added sugars" include a large "fudge-factor" based on total calorie consumption. Nonetheless, this recommendation is not dissimilar to other nutritional guidelines which recommend that a person consume 45 – 65% of their calories as carbohydrates.[1] Following the USRDA recommendations, if a woman consuming 1,700 calories per day were to consume 130 grams (520 calories) of carbohydrates and another 25% of her calories (425 calories) as *"added sugar,"* she would consume a total of 945 calories as carbohydrates, accounting for 55% of her daily calories. CDC data gathered from 2013 – 2016 estimated the average American consumes 47 – 49% of their calories as carbohydrates.[2] We believe that this level is too high for most people and is one of many factors contributing to obesity and other metabolic disorders in Western countries.

However, helping patients understand how to consume the correct types of carbohydrates (those with a low glycemic impact and a high amount of fiber) is much more important for long-term health than merely counting carbohydrate grams or calories. Even so, for those desiring carbohydrate counting advice, we believe maintaining total carbohydrate intake between 40 - 50% of total caloric intake (using low glycemic impact carbohydrates) is a good starting point for most individuals.[3] For those attempting weight loss or maintenance, we advise carbohydrate intake not to exceed 40%. Some low-carb diet plans may even suggest dropping carbohydrates to less than 20% of total calories, which is generally safe for most individuals for extended weight loss goals or managing blood glucose (though this may be too low for a sustainable long-term dietary plan).[4,5]

Carbs in Context

It is important to understand that although there are no unhealthy carbohydrate molecules, there are many unhealthy ways to consume carbohydrates. That is, carbohydrates of all kinds, when consumed with a balance of other nutrients (e.g., protein, fiber, fat, vitamins, phytonutrients) are rarely "bad" for our health. Problems arise when individuals consume high amounts of refined carbohydrates (e.g., refined flours, refined sugars, HFCS, etc.) with virtually no other nutrients to temper the body's glycemic response to those carbohydrates. Therefore, since the discussion of carbohydrate intake is often framed in terms of glycemic response, it is important to understand that this "signal" is defined in different ways.

Glycemic Index (GI): This number corresponds to the tested glycemic response, using healthy subjects, of a particular food portion containing a measured amount, typically 50 grams, of available carbohydrates (carbohydrates minus fiber), compared to the glycemic response of glucose (used as a control) in the same subjects. This calculated number is "indexed" to glucose, arbitrarily set as a GI of 100. Foods with a GI above 70 are usually considered high-GI foods, while those below 55 are considered low GI.

Glycemic Load (GL): This is essentially the measurement of the glycemic burden of a food based on the total amount of available carbohydrates per serving, multiplied by its GI. Glycemic load takes into account the fact that not all foods with a high GI contain high amounts of carbohydrates, like watermelon, while other foods, like a bagel, contain high amounts of high-GI carbohydrates creating a larger GL.

Glycemic Impact - What to Tell Patients: While there are debates as to whether glycemic load or glycemic index is more relevant to a person's glycemic response, few individuals are walking around with a scale and calculator to decipher the glycemic load of their meal. In the end, the goal is to reduce the glycemic *impact* of the meal by increasing the signal-to-calorie ratio, or here, the insulin-sensitizing signals to available carbohydrate ratio. The best way to do this is to give patients simple advice such as:

- Reduce or avoid added sugars and anything made with white flour
- Reduce or stop drinking sweetened (or artificially sweetened) soft drinks and juices
- Consume more fiber
- Eat food as close to its natural state as possible
- Have a handy list of high-glycemic index foods, read it, and avoid them
- Take a leisurely walk after a large meal

Artificial and Natural Non-Nutritive Sweeteners

While controversy remains about the risk and benefits of consuming *artificial* sweeteners such as acesulfame potassium, aspartame, saccharin and sucralose, we generally recommend they be avoided or severely limited by all individuals. Even though they are touted as low or no calorie options, obesity and type 2 diabetes appears to be more prevalent in subjects who consume more artificially sweetened beverages compared to subjects who do not.[6] Whether these compounds are acting physiologically or psychologically, leading users to indulge in more extravagant eating habits, has yet to be determined. Although less controversial, the role of "natural" non-nutritive sweeteners (e.g., stevia, monk fruit extract) is also unsettled in the minds of many health-minded consumers and physicians. Frankly, while the general use of these compounds has been shown to be safe, extensive research on subtle changes in long-term glycemic control or insulin sensitivity are lacking in most cases.

More challenging are the questions related to how the use of any sweetening agent reinforces the *"need for sweet"* craving to which individuals have grown all too familiar. There is a delicate balancing act between consuming products designed to deliver healthy ingredients, while offsetting the bitter or off-putting flavors with agents that are sweet on the tongue. The reality is, many patients will simply not consume products they do not like (e.g., taste, smell, mouthfeel, aftertaste, etc.). For this reason, we briefly overview some of the sweeteners commonly used in therapeutic products—functional foods, powders, bars and chewable tablets—available in many dietary supplements.

Fructose: Here we discuss the commercially-produced fructose ingredients used as added sugar for bars, powders and tablets, not natural fructose found in most fruits. Fructose is one of the most popular added sweeteners because it is sweet, has a natural mouth-feel, dissolves well, has a relatively low GI and is inexpensive. Fructose is also commonly recommended, over glucose and sucrose, as a *"diabetes-friendly"* sugar because it results in less post-prandial glucose and insulin compared to glucose and sucrose. However, regular and long-term consumption of fructose has been linked with insulin resistance, obesity, metabolic syndrome and diabetes.[7]

Because data on added fructose alone and that of high-fructose corn syrup (HFCS) are often combined, it is difficult to distinguish the health-related outcomes of one from the other. Therefore, we advise fructose to be used in moderation, and since other sweeteners are available, fructose should be limited when consuming products designed to promote health. Nearly all available commercial fructose is derived via a multistep process originating from cornstarch, although it may also be converted from cane or beet sugar, sucrose or, sometimes, directly from fruit juice sources. While GMO-free fructose is becoming more available, most fructose available in the United States is likely to be derived from a genetically-modified source.

Agave nectar (syrup): We list agave nectar here only because some of the marketing material for products containing agave-derived sweeteners imply it is low in calories. In fact, agave syrup is one of many natural sweeteners containing mostly fructose, which is lower in GI than glucose. We consider agave products to be similar in nature to honey and maple syrup, and do not consider agave to be worse than HFCS. As with other natural sweeteners, the total amount used and the context of the food containing the ingredient will determine its overall glycemic impact. Agave syrup, like honey or maple syrup, is often from organic sources.

Ingredient	Sweetness	GI	Cal/g
Sucrose (table sugar)	100%	60	4
Maltitol Syrup	75%	52	3
Hydrogenated Starch Hydrolysate	33%	39	2.8
Maltitol	75%	36	2.7
Xylitol	100%	13	2.5
Isomalt	55%	9	2.1
Sorbitol	60%	9	2.5
Lactitol	35%	6	2
Mannitol	60%	0	1.5
Erythritol	70%	0	0.2

Table 4: Comparing Polyol Sugars. Sweetness, Glycemic Index (GI) and calories per gram (US calculation) for polyol sugars used in foods and supplements. Data from: Livesey G. Health potential of polyols as sugar replacers, with emphasis on low glycaemic properties. *Nutr Res Rev.* 2003 Dec;16(2):163-91.

Vitamin B_1 (Thiamin)

Essential Nutrient Functions

Thiamin is a water-soluble vitamin that is recognized by many names including, thiamine, vitamin B_1 or aneurine. Isolated in the 1930s, thiamin was one of the first organic compounds to be characterized as a vitamin. In the human body, thiamin occurs as free thiamin and as various phosphorylated forms such as thiamin monophosphate (TMP), thiamin triphosphate (TTP) and thiamin pyrophosphate (TPP), where TPP is the active form. TPP is involved in several enzyme functions associated with metabolizing carbohydrates, fatty acids and branched-chain amino acids. Foods that are rich in thiamin include whole-grain cereals, nuts, legumes (e.g., lentils and beans), lean pork and yeast.

Supplemental Forms

- **Thiamin hydrochloride**
- **Thiamin mononitrate**
- **Benfotiamine (regulatory status vague)**

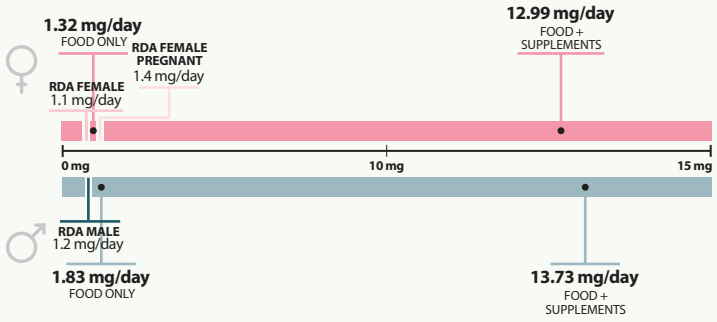
Vulnerabilities to Nutrient Inadequacy

Risk of Inadequate Intake

LOW | moderate | high

Standard American Diet: The risk of inadequate thiamin intake is relatively low considering intakes from all food sources (5% below EAR). However, excluding enriched/fortified foods creates a high risk of inadequate thiamin intake from naturally occurring sources alone (41.2% below EAR).

Average Intakes Compared to RDA from NHANES 2015 - 2016 for Individuals ≥ 20 Years



Additional Vulnerable Populations

Life Stage: Elderly

Lifestyle: N/A

Conditions: Malaria (Southeast Asia), HIV/AIDS, diabetes, bariatric surgery, alcohol abuse

Drug-Induced Depletion: Diuretics, phenytoin

Lab Tests for Nutrient Status

- Whole blood thiamin (TPP)
- Serum/plasma thiamin
- Urinary thiamin
- Transketolase activity

Special Notes

- Loop diuretics have been linked with increased urinary thiamin losses.
- If alcohol abuse becomes severe enough, thiamin status will likely continue to decrease and Wernicke-Korsakoff syndrome is likely to develop and cause extreme neuropsychiatric symptoms.

Recommended Intakes

The Food and Nutrition Board of the Institute of Medicine used a variety of measurements of thiamin status (e.g., erythrocyte transketolase activity, blood or serum thiamin and its phosphorylated esters, urinary thiamin excretion under basal conditions or after thiamin loading, etc.) to establish the Recommended Dietary Intakes for thiamin, which are based on the prevention of deficiency in generally healthy subjects.[1,2] The FNB noted in their analysis that no single indicator of thiamin status was adequate to determine the thiamin daily requirements. For infants 0 - 6 months and 6 - 12 months, an Adequate Intake was determined by the mean thiamin intake data from infants exclusively fed human breast milk and thiamin concentrations of milk produced by well-nourished mothers. The DV for adults and children > 4 years was recently decreased from 1.5 mg/day to 1.2 mg/day.

Thiamin Intake Guidelines (mg/day)

	RDA		DV
Age	Males	Females	All Individuals
0-6 mos	0.2 (AI)	0.2 (AI)	0.3
7-12 mos	0.3 (AI)	0.3 (AI)	
1-3 yrs	0.5	0.5	0.5
4-8 yrs	0.6	0.6	1.2
9-13 yrs	0.9	0.9	
14-18 yrs	1.2	1.0	
Adults 19+ yrs	1.2	1.1	
Pregnancy/Lactation 14+ yrs		1.4	1.4

Vulnerabilities to Inadequate Thiamin Status

Consuming the Standard American Diet

Thiamin deficiencies in the United States are relatively rare unless an individual suffers from the sequela of alcoholism. Inadequate consumption of thiamin due to malnutrition is usually the main cause of beriberi (clinical thiamin deficiency). Americans are thought to consume the RDA for thiamin, that is, 1.2 mg for adult men and 1.1 mg for adult women; though low-income populations (consuming diets low in thiamin and high in carbohydrates) have a higher prevalence of thiamin deficiency.[2] Illustrating this point, NHANES data from 2015 - 2016, show the mean reported intakes for thiamin in men and women (≥ 20 years) met or exceeded the RDA when reporting intakes from food only and food plus supplements.[3] Specifically, considering food alone (which includes enriched and fortified foods), men reported consuming 1.83 mg/day thiamin and women reported 1.32 mg/day; comparatively, when supplements are added, men reported consuming 13.73 mg/day and women reported consuming 12.99 mg/day thiamin.

When food sources are further differentiated, as was done in an analysis of NHANES data from 2009 - 2012, food enrichment and fortification were shown to play a large role in the relatively low prevalence of subjects below the EAR for reported thiamin intake.[4] Specifically, 41.2% of the NHANES population (≥ 2 years) reported thiamin intakes below the EAR from natural food sources, compared to 5% with fortification/enrichment and to just below 4% when both food (naturally occurring and enriched/fortified) and supplementation are taken into consideration. Similarly, an analysis of NHANES data from 2003 - 2006 echoed these results, suggesting that the enrichment/fortification of foods plays a large role in the relatively low prevalence of subjects below the EAR for reported thiamin intake.[5]

Other dietary factors may also affect thiamin status. Since the synthesis of thiamin triphosphate (TPP), the active form of thiamin, from free thiamin requires magnesium, functional deficiency of thiamin may be influenced by chronically low intakes of magnesium. Thiamin deficiency may also be caused by anti-thiamin factors which can be found in tea and coffee, including decaffeinated varieties.[2] Furthermore, cooking at high temperatures or at a high pH can denature thiamin, therefore proper food preparation is an important factor in retaining available thiamin for absorption.[6]

Life Stages Predisposing to Inadequate Thiamin Status

Elderly: According to NHANES data from 2009 – 2012, older adults (> 71 years) were twice as likely to report thiamin intakes below the EAR compared to a younger group (8.9% in > 71 years vs. 4.2% in 19 – 50 years) from food intake alone.[7] With the addition of dietary supplementation, these numbers dropped to 5.3% in the > 71 age group and 3.5% in 19 – 50 year-olds.[7] Older adults generally consume less food, are more susceptible to chronic diseases, use multiple medications and present with lower absorption capabilities, thus predisposing the elderly to inadequate nutrient status.[8]

Health Conditions Predisposing to Inadequate Thiamin Status

Malaria: Thiamin functions as a cofactor in the metabolism of glucose and this demand is increased in those with malarial infections. Thiamin deficiency was found in patients (N = 310) with malaria in Laos but was reduced with proper medication and use of a multivitamin.[10]

HIV/AIDS: Individuals with HIV/AIDS are at an increased risk of thiamin deficiency, including its sequelae (e.g., beriberi, Wernicke-Korsakoff syndrome), most likely due to malnutrition.[8] In the past, Boldorini et al. found that almost 10% of AIDS patients had Wernicke's encephalopathy, indicating thiamin deficiency.[11] In addition, Muri et al. studied thiamin status in HIV-positive patients (N = 55) and found an increased risk for thiamin deficiency, independent of the development of AIDS.[12]

Diabetes (Types 1 and 2): A small study investigated thiamin status in both type 1 (N = 26) and type 2 (N = 48) diabetic patients by analysis of plasma, erythrocytes and urine. Compared to non-diabetic controls, plasma thiamin levels were 76% and 75% lower in type 1 and type 2 diabetic patients, respectively ($P < 0.001$).[13] Low plasma thiamin concentration was associated with both fractional excretion of thiamin ($P < 0.001$) and renal clearance of thiamin ($P < 0.001$). Analysis of the urinary excretion of thiamin in type 1 and type 2 diabetic patients showed a fourfold and threefold increase, respectively, compared to healthy controls ($P < 0.001$). Interestingly, when assessing the transketolase activity of erythrocytes, a significant difference was not seen between healthy controls and the diabetic population. In contrast, a different study showed diabetic patients were at risk for thiamin deficiency (N = 46) based on thiamin transketolase activity.[14] While there is still some debate about the relationship between diabetes and thiamin status, clinicians should keep this relationship in mind considering the importance of this nutrient for carbohydrate metabolism.[15,16]

Bariatric Surgery Patients: Because of the risk of malabsorption after bariatric surgery, micronutrient supplementation, including thiamin, is often recommended to help patients avoid nutrient deficiencies.[17] A 2008 systematic review found that gastric bypass surgery was associated with Wernicke's encephalopathy, a severe consequence of thiamin deficiency accompanied by vomiting, nystagmus (repetitive, uncontrolled movements of the eye) and poor coordination of posture and gait in more than half of the gastric bypass patients studied.[18]

Alcohol Abuse: Those who abuse alcohol are particularly vulnerable to thiamin deficiency and should be monitored closely by healthcare professionals when possible. It is estimated that the prevalence of thiamin deficiency in subjects with chronic alcoholism ranges from at least 25% up to 80%, depending on the study.[8,9] This deficiency may be simply due to inadequate intake of essential nutrients; however, once advanced stages of alcohol dependency have been reached, ethanol can directly cause impaired thiamin absorption in the gastrointestinal tract, deplete thiamin liver stores and reduce the phosphorylation of the active form of thiamin, TPP.[8]

Drug-Induced Nutrient Depletion

Diuretics: In the recent past, studies have shown that diuretic use increases urinary excretion of thiamin, especially with the use of furosemide.[19,20,21]

Anti-Convulsant Medications (e.g., phenytoin): Work completed by Botez et al. on long-term phenytoin medication use (≥ 10 years) showed that there was a significant difference between blood thiamin ($P < 0.001$) and cerebral spinal fluid thiamin ($P < 0.001$) in subjects taking phenytoin (N = 11) compared to a control group (N = 23).[22] Although the details of the mechanism underlying phenytoin and low thiamin status are not well understood, Patrini et al. discovered that chronic treatment (30 days) of phenytoin in rats interfered with thiamin and TMP uptake, TPP conversion to TMP and TPP turnover times.[22]

Oral Contraceptives: Although the use of oral contraceptives may be associated with slight to moderate decreases in thiamin status, there is insufficient evidence to make a firm association.[23] In general, coadministration of oral contraceptives with a multivitamin that contains B-vitamins may safely and effectively reduce the risk of oral contraceptive-associated thiamin insufficiencies.[23]

Lab Tests for Nutrient Status

Whole Blood Thiamin (TPP): The concentration of thiamin pyrophosphate (TPP) in erythrocytes decreases with declining thiamin status at a similar rate as other tissues,[1] which makes this a preferred method of thiamin measurement; however, this test has low specificity and sensitivity. It should be noted that under conditions of systemic inflammation, blood thiamin may be falsely reduced.[24] Although the normal range of blood thiamin varies between laboratories, it is approximately 70 to 180 nmol/L (3.0 to 7.7 µg/dL).[6,25,26] According to the Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes and its Panel on Folate, Other B Vitamins, and Choline, erythrocyte thiamin values between 70 and 90 nmol/L indicate marginal thiamin deficiency and values less than 70 nmol/L suggest deficiency.[1,6,25,26]

Serum/Plasma Thiamin: Thiamin is often measured by assessing plasma or serum concentrations, although plasma thiamin only reflects recent dietary intakes, rather than body stores. The biologically active form of thiamin, TPP, is not found in plasma in measurable amounts; therefore, using an additional test like whole blood thiamin is recommended and will aid in clinical decision making.[27] The normal range of plasma thiamin varies between laboratories, but it is approximately 4 to 15 nmol/L.

Urinary Thiamin: Urinary thiamin excretion, which provides data on recent dietary intakes of thiamin (not tissue levels) is a commonly used measure to assess thiamin status in populations, though it has several limitations. As thiamin status declines, urinary thiamin excretion also decreases, and insufficient thiamin intake is noted if urinary excretion is < 100 µg/day.[1,8] A urinary thiamin loading test can be used to further evaluate thiamin status and differentiate between extremes in status.[1] In this test, urinary excretion is measured before and after a test dose of thiamin.

Erythrocyte Thiamin Transketolase Activity (ETKA): The erythrocyte thiamin transketolase activity test is an indirect and functional measure for thiamin status. In this test, erythrocytes are lysed and the transketolase activity, which depends on thiamin pyrophosphate (TPP), is measured before and after TPP is added as a stimulus *ex vivo*.[1] Those with thiamin deficiency show low transketolase activity at baseline and increases between 20 and 25% in transketolase activity after TPP stimulation. Healthy individuals typically have an increased thiamin transketolase activity following stimulation with TPP of 0 – 15%.[6] Some studies have found inconsistencies between thiamin intake and results of the ETKA test; therefore, it is recommended to use this test along with other indicators of thiamin status.[1,28] Further, genetic factors may influence the enzymatic activity and, consequently, the result of this test.[1]

Symptoms of Thiamin Deficiency

While severe clinical deficiency of thiamin (beriberi) is infrequently diagnosed in Western subjects, there are many factors that contribute to thiamin deficiency, including inadequate thiamin intake, excessive thiamin loss from the body, increased thiamin requirements, consumption of anti-thiamin factors found in food or a combination of these factors.[2]

Mild symptoms of thiamin deficiency are non-specific and may include weight loss, anorexia, changes in mental status, memory problems and cardiovascular effects.[1] When thiamin deficiency becomes more severe (beriberi) symptoms manifest based upon which subgroup of beriberi is present: dry beriberi, wet beriberi, cerebral beriberi or gastrointestinal beriberi. The main characteristics of dry beriberi include neuropathy, which may be predisposed by "*burning feet syndrome.*" Wet beriberi is characterized by cardiovascular symptoms (e.g., edema, difficulty breathing, rapid heart rate, enlarged heart, etc.) along with neuropathy.[2] More common in people who abuse alcohol, Wernicke-Korsakoff syndrome (made up of Wernicke's encephalopathy and Korsakoff's psychosis) may develop with severe thiamin deficiency, which affects the nervous system, as well as memory and cognition.[8] Since TPP is needed for glycolysis and the TCA cycle, a decrease in thiamin availability can cause pyruvate and lactate accumulation leading to symptoms of gastrointestinal beriberi, a condition causing nausea, vomiting and abdominal pain.[2]

Potential for Toxicity

Thiamin has no known toxicity and the upper tolerable limit has not been determined by the IOM.

Drug-Induced Nutrient Depletion

Aminoglycoside Antibiotics (e.g., gentamicin): To date, the research evaluating the effect of the aminoglycoside antibiotic, gentamicin, on vitamin B_6 status has been performed in animal models (e.g., rats and rabbits). These findings suggest that gentamicin forms complexes with pyridoxal 5' phosphate (PLP), interfering with vitamin B_6 metabolism.[22]

Antiparkinsonian Drugs (e.g., carbidopa, levodopa): Carbidopa and levodopa are both commonly used in the treatment of Parkinson's disease. PLP is a cofactor in the conversion of levodopa to dopamine. Increased levels of levodopa can increase the metabolic requirement of pyridoxine.[22] Carbidopa has been shown to deactivate free PLP and all of the PLP-dependent enzymes, which negatively impacts the function of PLP-dependent enzymes and proteins.[23,24]

Erythropoiesis-stimulating Agents (e.g., EPO): Patients undergoing dialysis treatment have been shown to be vulnerable to pyridoxine deficiency due to the need for increased stimulation of hemoglobin synthesis.[22] Pyridoxine supplementation at a dose of 20 mg/day is suggested for these patients.[25]

Hydralazine: Hydralazine is thought to act as a pyridoxine antagonist, which works to inhibit a number of enzymes and may increase vitamin B_6 requirements.[22,26]

Loop-diuretics (e.g., furosemide): Furosemide is a loop-diuretic and is often prescribed to help in the management of hypertension. In patients receiving 20 mg furosemide (intravenously), urinary clearance of vitamin B_6 was increased in patients with chronic kidney failure.[27]

Oral Contraceptives: Data from NHANES (2003 - 2004) found that 75% of women who were actively taking oral contraceptives without dietary supplementation had reduced plasma pyridoxal 5' phosphate (PLP) concentrations (< 20 nmol/L).[8] Administration of pyridoxal in doses of 10 – 400 mg/day (dependent upon case) has been shown to be effective in ameliorating symptoms associated with oral contraceptive use.[22]

Theophylline: Pyridoxal kinase, the enzyme needed to convert vitamin B_6 to its active form, pyridoxal 5' phosphate (PLP), is inhibited by theophylline. One study found the administration of theophylline to asthmatic patients resulted in vitamin B_6 deficiency.[22] Later, a study investigating this relationship in healthy, young men found reduced plasma PLP levels in the group receiving theophylline (N = 17) compared to placebo (N = 15) in just one week (37.7 nmol/L compared to 50.0 nmol/L, respectively; P = 0.058). Compared to placebo, concentrations of plasma PLP continued to decrease in the theophylline group significantly (P < 0.001). This interaction was ameliorated by supplementation with 10 mg pyridoxine starting at week five.[28]

Lab Tests for Nutrient Status

Direct Indices of Vitamin B_6 Status

Plasma/Serum Vitamin B_6 (aka plasma pyridoxal 5' phosphate (PLP)): Vitamin B_6 status is commonly assessed by measuring the concentrations of vitamin B_6 in the circulation, namely, as pyridoxal 5' phosphate (PLP) in the plasma.[29] Plasma PLP shows a positive association with recent vitamin B_6 intake and is strongly correlated to liver PLP; but results may be skewed due to inflammation, alcohol consumption, albumin concentration and alkaline phosphatase activity.[30] These nuances have recently been reviewed by Ueland et al.[31] Reference ranges for plasma PLP are fairly wide: 5.3 – 46.7 ng/mL for men and 2.0 – 32.8 ng/mL for women, though each lab may report a slightly different range (to convert ng/mL to nmol/L, multiply by 4). Mild insufficiency is noted at plasma PLP levels < 20 nmol/L (< 5 ng/mL). Erythrocyte PLP levels are actually considered to be a better biomarker of vitamin B_6 status as PLP serves as an intracellular cofactor, though the test itself (and published references ranges) are currently less reliable.[32]

Urinary 4-Pyridoxic Acid (PA): 4-pyridoxic acid (PA) represents the major metabolic species (> 90%) of vitamin B_6 excreted in urine and is an excellent indicator of recent dietary or supplemental intake of vitamin B_6.[33] Urinary PA is thought to be best utilized in combination with other markers reflecting metabolic alteration which can provide more accurate assessment of nutritional vitamin B_6 status and intake.[31] Reference ranges differ, based on lab availability and test used (i.e., single random urinary test or 24-hour urine test) but urinary PA excretion > 3 µmol/day indicates adequate short-term vitamin B_6 status from a random sample.[32] Plasma PA can also be used to measure vitamin B_6 status, but it is confounded by several factors including kidney clearance of PA.

Functional Vitamin B_6 Biomarkers

Erythrocyte Transaminase Activity: Transaminases or aminotransferases are important PLP-dependent enzymes. The activities of the enzymes erythrocyte alanine transaminase (EALT) and erythrocyte aspartic acid transaminase (EAST) are functional biomarkers of vitamin B_6 status, which reflect long-term erythrocyte vitamin B_6 status and correlate with the lifespan of red blood cells.[32] Assay results are reported as an activity coefficient (AC), which is calculated by comparing the enzyme activity before and after the addition of PLP.[31] Next, the percentage stimulation can be calculated from the AC. A higher AC reflects greater difference in activity when the additional PLP is supplied and is indicative of a lower baseline vitamin B_6 status. Standardization is needed for using either assay.

Plasma Kynurenines: The enzymes involved in tryptophan catabolism, kynurenine transaminase (KAT) and kynureninase (KYNU) require pyridoxal 5' phosphate (PLP) as a cofactor and produce two end-stage metabolites: kynurenic acid (KA) and xanthurenic acid (XA). Both plasma and urinary concentrations of these metabolites have been evaluated as functional markers of vitamin B_6 status due to the involvement of PLP as a cofactor.[31] Specifically, after a tryptophan challenge, if vitamin B_6 deficiency is present, XA levels will be elevated. Normally, XA is < 65 µmol/day following a 2 g tryptophan load.[32]

Symptoms of Vitamin B_6 Deficiency

Clinical vitamin B_6 deficiency is uncommon since it is available in many food sources but if it does occur, deficiency is usually accompanied with other B-vitamin deficiencies.[29] Individuals with certain conditions may be at an increased risk for vitamin B_6 deficiency. Symptoms of vitamin B_6 inadequacy do not appear until status of inadequacy is severe and may include irritability, depression, and confusion. Signs of severe vitamin B_6 deficiency includes angular cheilosis, inflammation of the tongue and microcytic anemia.[34]

Potential for Toxicity

Even though vitamin B_6 is water soluble, toxicity of this nutrient from supplements has been documented at high doses. The IOM has set the tolerable upper limit for supplemental vitamin B_6 at 100 mg/day in adults.[34] The IOM noted that, though several case reports show sensory neuropathy occurring at doses lower than 500 mg/day, studies in patients treated with vitamin B_6 at an average dose of 200 mg/day for up to five years found no evidence of this effect.[35] However, the European Food Safety Authority (EFSA) has set the safe upper limit for daily supplementation at 25 mg/day, citing case studies of apparent toxicity at lower doses.[36]

A recent *in vitro* study comparing the neurotoxic effects of each vitamin B_6 vitamer on SHSY5Y (neuroblastoma) cells showed that pyridoxine, but not P5P, was capable of inducing cell death in a dose-dependent fashion; and that P5P, when added to pyridoxine, was able to partially ameliorate this effect.[37] Though these data are limited to this cell type alone, the authors speculate that the passive absorption of high oral doses of pyridoxine could be responsible for vitamin B_6-related toxicity/neuropathy by allowing unphosporylated pyridoxine to competitively inhibit the actions of cellular pyridoxal phosphate. Unpublished data from this same group show that a 50 mg dose of pyridoxine may increase serum unphosphorylated pyridoxine in some subjects (Geja Hageman, PhD, email correspondence 5/19/2019).

Whether these data are enough to suggest that P5P is safer (i.e., less likely to cause neuropathy in susceptible subjects) than pyridoxine HCl when taken at doses above 25 mg is yet to be determined. The cost difference between these two substances is quite substantial and numerous clinical trials using very high doses (>200 mg/day) of pyridoxine have been reported with no side effects, making the routine adoption of P5P for high-dose therapy difficult. However, routine use of vitamin B_6 supplementation above 25 mg/day is mostly unneccessary, except when using a therapy known to be effective and safe.[38]

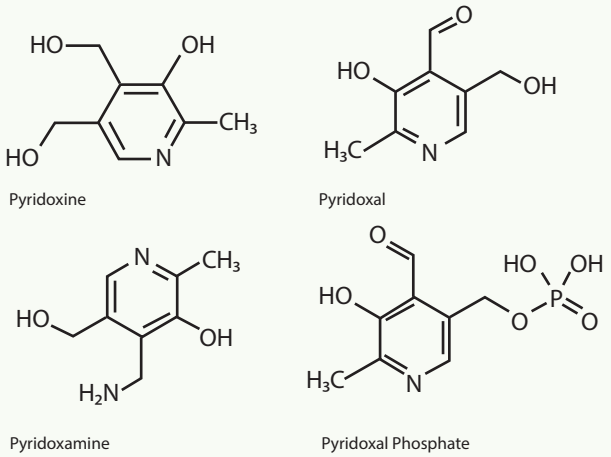
Supplemental Forms

Food sources contain vitamin B_6 in all three forms—pyridoxine, pyridoxamine, pyridoxal—as well as in their phosphorylated and glucoside-conjugated forms. All phosphorylated compounds must be hydrolyzed into their respective unphosphorylated forms prior to absorption in the small intestine, after which *in vivo* conversion allows each to act as vitamin precursors.[39] Phosphorylation of the coenzyme form occurs as needed in the liver.[40] Pyridoxine produced by human gut microbiota, followed by colonic absorption, may also contribute to overall vitamin B_6 status.[41]

The primary vitamin B_6 ingredient used for food fortification and dietary supplements is the synthetic "*bioequivalent*" compound pyridoxine HCl.[29] This compound has been shown to have higher bioavailability than food-source vitamin B_6, due to the reduced gastrointestinal hydrolysis of some (mostly plant) glucoside conjugates.[42]

Some estimates suggest synthetic supplemental pyridoxine is 1.27 times more bioavailable (95%) compared to food source pyridoxine (75%).[1] Interestingly, Roth-Maier et al. discovered that the bioavailability of vitamin B_6 from both plant and animal foods is between 51 to 91%, whereas the bioavailability from plant sources was on average 10% lower compared to the bioavailability of vitamin B_6 from animal sources.[43]

It is common for some supplement manufacturers to use pyridoxal-5-phosphate (PLP or P5P) and market this ingredient as an *"active"* or *"natural"* form of supplemental vitamin B_6. While also being *"bioequivalent,"* this supplement ingredient is synthesized from pyridoxine or pyridoxamine precursors, which increases its cost significantly. When taken orally, P5P must be dephosphorylated prior to absorption and, therefore, has similar or lower bioavailability compared to pyridoxine. In terms of supplementation and fortification to reach adequate vitamin B_6 status (< 50 mg/day), these compounds should be considered therapeutically equivalent. See discussion above (toxicity) for potential differences between the toxicities of these compounds. Pyridoxamine has also been available as a dietary supplement in the United States. However, the US FDA has deemed that this compound cannot be used as a dietary supplement ingredient, as this compound is still undergoing investigation as a drug.



Vitamin B_6 Chemical Structures

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A Balanced and Evidence-Based Approach

The use of dietary supplements continues to grow and is a fundamental health-promoting strategy to bridge the gap between a person's nutritional needs and their actual dietary intake. In addition, thousands of forward-thinking healthcare professionals routinely recommend dietary supplements to optimize their patient's nutrient status. However, clinicians and patients are routinely faced with an onslaught of confusing, contradictory, over-hyped and often misleading information about nutrition, especially dietary supplementation, preventing them from fully leveraging the potential of dietary supplementation. Unfortunately, many nutritional guideline recommendations and references are decades old and out-of-sync with the latest nutritional research; and most lack the practical and clinically-relevant relationship linking the evidence-based science of nutrition with the actual ingredients and products available to consumers in the real world. *Supplementing Dietary Nutrients—A Guide for Healthcare Professionals - Second Edition* continues to bridge this gap.

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