REVIEW ARTICLE

NUTRITION IN MEDICINE
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Micronutrients — Assessment, Requirements, Deficiencies, and Interventions

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There are approximately 20 essential micronutrients, and deficiency in one or more has distinct effects on the metabolome, proteome, and genome. Since basic information about micronutrients is available in textbooks, reports on the ways in which requirements were established,[1] reviews, and websites,[2] the main purpose of this article is to provide an overview of current issues in micronutrient assessment, interventions, and research that are of interest to health care practitioners. In the United States, the prevalence of most micronutrient deficiencies is low. National surveys — namely, the National Health and Nutrition Examination Survey (NHANES), which assesses biochemical markers of nutritional status, as well as its interview component, What We Eat in America, which measures nutrient intakes — provide some data on micronutrient status in the general population. However, these measures are made cross-sectionally, so it is difficult both to infer causality between micronutrient deficiencies and chronic diseases and to assess the health benefits of interventions such as supplementation. In recent decades, there has been a concerted international effort to study micronutrient deficiencies and interventions in low- and middle-income countries and population groups in which the prevalence and severity of most deficiencies are highest. One third of the world's population has one or more micronutrient deficiencies.[3,4]

HISTORICAL DEVELOPMENT

Micronutrients are defined as nutrients that are essential for health and survival, but in trace amounts. They are categorized as water-soluble and fat-soluble vitamins and trace minerals (required in amounts of <100 mg per day). Macrominerals, including calcium and sodium, are usually excluded from the micronutrient category. Historically, the importance of micronutrients was recognized because relatively severe deficiencies cause serious clinical symptoms, but it took centuries for the specific nutrients to be identified in most cases. Among the many examples are vitamin C (ascorbic acid) deficiency, which caused scurvy in seafarers who lacked access to fresh food and which killed more than 2 million people between the 16th and 18th centuries; vitamin D deficiency, which leads to rickets, a condition that was recognized in the 1600s and became more prevalent during the Industrial Revolution in western Europe as a result of air pollution and inadequate exposure to sunlight; thiamine deficiency, which results in beriberi and was associated with consumption of polished rice; vitamin A deficiency, which causes night blindness and xerophthalmia; and deficiencies of iron and vitamin B_{12}, which lead to anemias.[5]

KEY POINTS

MICRONUTRIENT ASSESSMENT, DEFICIENCIES, AND INTERVENTIONS

- Inquiry about the usual dietary pattern, with a focus on the omission of specific foods that can increase the risk of inadequate intake of micronutrients, is an important part of the assessment of micronutrient status.
- Micronutrient deficiencies, especially those identified on the basis of laboratory assessment, are generally uncommon in the United States.
- In addition to low dietary intake, certain clinical factors (e.g., malabsorption, intestinal surgery, alcoholism, some medications, anorexia, and pernicious anemia) increase the risk of micronutrient deficiency.
- Dietary and biochemical assessments are complementary, and there are reasons why they may not always be in agreement.
- Because national data on micronutrient intakes and status are collected cross-sectionally, it is difficult to determine the extent to which deficiencies are causal factors for chronic diseases and poor health.
- Randomized, controlled trials are needed to test the benefits of supplementation, but few of these trials have shown clear benefits in the United States.
- Future research should include more sensitive and informative methods of assessment for micronutrient deficiencies, such as “omics,” to detect effects on metabolism, gene expression, and proteins.

It was not until the early 20th century that the term “vitamin” was applied to the factors that caused these clinical symptoms. The fascinating process of discovery lasted for more than a century and was based on animal models, synthesis of vitamins by chemists, and the finding that vitamins could prevent and cure the symptoms of deficiency.[5] However, the adverse effects of milder micronutrient depletion in the absence of clinical symptoms was not generally recognized until the 1980s. Since that time, a growing number of large, randomized, controlled trials, especially in low- and middle-income countries, have revealed the importance of adequate micronutrient status and the efficacy and effectiveness of interventions. This evidence has encouraged most countries in the world to develop micronutrient surveillance and control programs.

REQUIREMENTS

The recommended intakes of vitamins and minerals are established in several ways, but a process for setting requirements is now recommended by authorities such as the National Academies of Sciences, Engineering, and Medicine (NASEM), for the United States and Canada,[6] and the European Food Safety Authority (EFSA). Three primary nutrient reference values have been determined for each of approximately 22 population groups defined on the basis of age, sex, and pregnancy and lactation status: the estimated average requirement (EAR), which is the median requirement for a group; the recommended dietary allowance (RDA), which is the amount sufficient to cover the needs of 97.5% of a group and is based on the EAR plus 2 SD (usually 20%); and the tolerable upper intake level, which is the highest average intake level that is likely to have no adverse health effects. The tolerable upper intake level is especially useful in the case of micronutrients because it applies to long-term daily use of supplements and fortified foods. A fourth value, adequate intake, is used when the EAR or RDA cannot be determined. This is a suboptimal situation because the EAR is the value used to assess the percentage of people who have inadequate intake within population groups and to determine the type and level of micronutrient interventions needed. Both NASEM and EFSA provide EAR and upper intake values for most nutrients, but a substantial number of EARs are lacking because average intakes were estimated instead. A “harmonized” set of nutrient reference values — mainly a combination of the values in NASEM and EFSA reports — has been proposed[7] and was recently used to estimate the prevalence of inadequate micronutrient intake nationally and subnationally.[8]

For nutrients with an EAR and an RDA, a reported intake below the EAR should be increased because the probability of inadequacy is 50%. If

Table 1. Biomarkers of Micronutrient Status.*

Nutrient	Biomarker	Cutoff Value for Inadequacy or Other Status	Adjusted for Inflammation	Comments
Vitamin A	Serum retinol	<0.7 μmol/liter	Yes	Levels relatively insensitive to changes in status; deficiency rare in the United States
Vitamin D	Serum 25(OH)D	<30 nmol/liter	No	Alternative cutoffs are <25 nmol/liter for severe deficiency and 25–50 nmol/liter for insufficiency
Vitamin E	Serum α-tocopherol	<12 μmol/liter	No	Alternative cutoff is <30 μmol/liter on the basis of levels associated with lowest mortality in ATBC; level of <12 μmol/liter is rare in the United States
Thiamine (vitamin B_1)	ETK activity coefficient	Status considered marginal if addition of TDP increases ETK level by 15–25%, deficient if increase is >25%	No	No plasma assay; urinary thiamine level reflects recent intake; 100 μg/day is considered insufficient intake; deficiency is rare in the United States except in association with alcoholism
Riboflavin (vitamin B_2)	EGRAC	1.2–1.4 considered low; >1.4 considered deficient	No	No plasma assay; use of red-cell riboflavin level of <170 nmol/liter detects 92% of cases of deficiency with EGRAC of ≥1.4†; prevalence of deficiency uncertain in the United States but high in Europe if dairy avoided
Niacin (vitamin B_3)	Urinary N1-methylnicotinamе plus N1-methyl-2-pyridone-5-carboxamide	<5.8 μmol/day	No	5.8–17.5 μmol/day is considered low; deficiency is rare in the United States
Pyridoxine (vitamin B_6)	Plasma pyridoxal phosphate	<20 or <30 nmol/liter	No	NAM cutoff of <20 nmol/liter used to set requirements, but <30 nmol/liter more commonly used[1]; low values in approximately 20% of NHANES participants
Folate (vitamin B_9)	Red-cell folate	<400 nmol/liter		Serum folate level of <6.8 nmol/liter also indicates deficiency but is affected by recent intake; serum homocysteine level of <12–16 μmol/liter indicates deficiency but is affected by B_{12} status; low values now rare in the United States
Vitamin B_{12}	Serum or plasma cobalamin	<221 pmol/liter	No	<150 pmol/liter indicates deficiency, <221 pmol/liter indicates marginal status; serum holotranscobalamin ("active B_{12}") more sensitive, slightly more specific, and reflects recent absorption; serum MMA level of >0.27 μmol/liter can confirm deficiency, but levels are also elevated by renal insufficiency

Iron	Serum ferritin	<30 μg/liter	Yes	<10 μg/liter indicates risk of iron deficiency anemia; ferritin level is reduced before hemoglobin level; greatly increased by inflammation
Zinc	Plasma zinc	<11 μmol/liter	Yes	<10.4 μmol/liter indicates deficiency in women, <11.0 μmol/liter indicates deficiency in men; value is lower if inflammation present
Iodine	Urinary iodine	<100 μg/liter; <150 μg/liter during pregnancy	No	Urinary iodine is used as a marker of intake at the population level; thyrotropin level is elevated when intake less than approximately 100 μg/day

* Data are from fact sheets issued by the National Institutes of Health (NIH) Office of Dietary Supplements, among other sources. The values are for adults. Detailed information on vitamin A, vitamin D, folate, vitamin B_{12}, zinc, and iodine status and assessment is provided in the NIH series Biomarkers of Nutrition and Development. 25(OH)D denotes 25-hydroxyvitamin D; ATBC Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; EGRAC erythrocyte glutathione reductase activity coefficient; ETK erythrocyte transketolase; MMA methylmalonic acid; NAM National Academy of Medicine; NHANES National Health and Nutrition Examination Survey; and TDP thiamine diphosphate.

† The information on riboflavin deficiency is from Graham et al.[9]

the intake increases above the EAR, the risk of inadequacy falls and reaches 2 to 3% at the RDA level. The RDA is used to plan diets for healthy persons, and because it is set to cover the needs of almost everyone, it leads to a substantial overestimate of the prevalence of micronutrient inadequacy if applied to a population group.

ASSESSMENT

Assessment of micronutrient adequacy is usually based on intake from foods and other sources, biochemical indicators (biomarkers), or both. These approaches often produce different estimates of risk and status, but both are useful, and they can be complementary. The different estimates may be explained by nonrepresentative or inaccurate dietary data collection, errors in food composition tables, errors in estimates of requirements, or poor absorption from the diet as a result of disease or other factors.

Biomarkers of micronutrient status have generally agreed-on cutoff values that designate deficiency or, in some cases, depletion or marginal status (Table 1). However, the biomarkers for some micronutrients (e.g., zinc) are still rather poor, and the serum or plasma levels of other micronutrients (e.g., serum retinol) are homeostatically controlled. The values for cutoff values that indicate deficiency or depletion are sometimes debatable and should be set as ranges. Requirements for vitamin D are based on the assumption of low exposure to ultraviolet light, but the level of ultraviolet light exposure, the season of the year, and skin pigmentation are usually more important factors than intake from foods. As shown in Table 1, several biomarkers must be corrected for inflammation with the use of markers such as C-reactive protein or α1-acid glycoprotein. The BRINDA (Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia) research group recently proposed a practical way to adjust for inflammation,[10] which in the United States would be useful mostly for correction of serum ferritin and plasma zinc concentrations.

Assessing the adequacy of micronutrient intake presents specific challenges because of the large number of micronutrients, lack of food composition values, and intake of micronutrients from the widespread consumption of fortified foods and supplements. Information on dietary patterns can be very useful because some nutrients of concern cluster in food groups. For example, animal-source foods provide most of the preformed vitamin A, vitamin B_{12}, absorbable iron and zinc, thiamine (vitamin B_1), riboflavin (vitamin B_2), pyridoxine (vitamin B_6), and choline in unfortified diets, so low intakes of these foods can predict a reduced consumption of all these micronutrients. This is especially evident in low- and middle-income countries where there is a higher reliance on staples. Dietary iron and zinc requirements can be higher for persons who consume a vegan or vegetarian diet because of the lower bioavailability (absorbability) of these nutrients from such diets. Although a recent systematic review concluded that there are no dietary biomarkers that can identify individual dietary patterns,[11] identification of any food groups that are avoided by study respondents can be very helpful in determining the risk of micronutrient deficiencies and should be a priority.

The National Institutes of Health web-based Automated Self-Administered 24-hour (ASA24) Dietary Assessment Tool, which is free, enables interviewees or dietitians to enter data from 24-hour recall or food diaries.[12] With this tool, more than one day of data can be collected. Ideally, at least 2 days of intake data should be collected several days apart to reduce error due to day-to-day variation in intakes, which can be considerable for micronutrients that may be consumed in large amounts but infrequently (e.g., vitamin A). The output includes data on 13 vitamins, iron, selenium, and zinc but no other trace elements. A total of 37 food groups are also analyzed. Since 2016, the ASA24 has allowed for entry of data on supplements, including micronutrient supplements.

MICRONUTRIENT STATUS IN HIGHER-INCOME POPULATIONS

The Office of Dietary Supplements, supported by the National Institutes of Health, is a reliable source of information on micronutrient requirements and sources, as well as the safety and usefulness of dietary supplements in the U.S. population. The fact sheets for professionals issued by the Office of Dietary Supplements have more detailed information than is possible to provide here.[2] The Dietary Reference Intake Calculator for Healthcare Professionals[13] and the Department of Agriculture food composition data[14] are available online. In the case of micronutrients, it is important to recognize that many foods are fortified with micronutrients, and supplement intake is common.

The Office of Dietary Supplements states that supplements that can improve health in the United States include calcium and vitamin D to reduce bone loss, folic acid (ideally with supplementation starting before conception) to lower the risk of birth defects such as spina bifida, omega-3 fatty acids to reduce heart disease, and a mix of vitamins C and E, copper, zinc, lutein, and zeaxanthin to slow age-related macular degeneration. At-risk persons and population groups are those that exclude certain foods or food groups from their diet (e.g., persons who adhere to a strict vegetarian diet need supplemental sources of vitamin B_{12}, and persons who avoid dairy products need other sources of riboflavin, calcium, and vitamin D).

An analysis of NHANES surveys from 2007 to 2014 that used the ASA24 method estimated intakes of 18 nutrients, including micronutrients, by persons who were 51 years of age or older.[15] Among persons who did not use multivitamin–mineral supplements, less than 5% had inadequate intakes of copper, iron, and selenium, and only 25% consumed too little zinc. Choline intake was less than the EAR in 90% of persons, vitamin C in 45%, vitamin D in 100%, and vitamin K in 55%. On the basis of biomarker values in nonusers, however, only vitamin B_6 and D deficiencies were found in a substantial percentage of survey respondents: across age groups, 16 to 23% of respondents had vitamin B_6 deficiency, 26% had vitamin D inadequacy and 5 to 7% had deficiency, and approximately 2 to 4% had vitamin B_{12} deficiency. (Iron status was not included because iron deficiency is rare among older adults.) There has been little effort to follow up on the surprisingly high prevalence of low vitamin B_6 status. Use of multivitamin–mineral supplements increased levels of vitamin B_6, vitamin D, folate, selenium, iodine, and vitamin B_{12} but not serum iron, copper, or zinc. With multivitamin–mineral supplementation, a low percentage of calcium, folic acid, zinc, and selenium intakes exceeded the tolerable upper level.

From another perspective, a recent global analysis showed that 1 in 2 women in the United

Kingdom and 1 in 3 in the United States have at least one micronutrient deficiency on the basis of biomarker data. The most common deficiency was iron, which affects 20% of women in both countries.[3]

MICRONUTRIENTS OF CONCERN IN THE UNITED STATES

In a 2018 position paper on micronutrient supplementation, the Academy of Nutrition and Dietetics stated, “[M]icronutrient supplements are warranted when requirements are not being met through the diet alone. Those with increased requirements secondary to growth, chronic disease, medication use, malabsorption, pregnancy and lactation, and aging may be at particular risk for inadequate dietary intakes. However, the routine and indiscriminate use of micronutrient supplements for the prevention of chronic disease is not recommended, given the lack of available scientific evidence.”[16] Nevertheless, more than half of adults use at least one dietary supplement, mainly micronutrient supplements. Figure 1 shows the risk factors for micronutrient deficiencies in the United States.

Supplement users — both adults and children — are healthier and consume higher-quality diets than nonusers. The most common supplements are multivitamin–mineral supplements and vitamin D, calcium or vitamin D plus calcium, vitamins B_2 and B complex, and vitamin C. Persons who take these supplements believe that they improve health. Approximately 75% of pregnant women take a multivitamin–mineral supplement. Micronutrient requirements are even higher during lactation than during pregnancy, and the concentrations of most vitamins and a few minerals (e.g., selenium and iodine) in breast milk are affected by maternal diet and supplements.[17] Fortified breakfast cereals are an important source of micronutrients, especially for children. It is important to recognize that correcting micronutrient deficiencies by improving diet can be a relatively slow process as compared with supplementation and fortification.

VITAMIN D

Vitamin D deficiency is one of the most common micronutrient deficiencies in the United States. An analysis of data from 71,685 participants in NHANES (2001 to 2018) showed that vitamin D levels were less than 25 nmol per liter, 25 to 50 nmol per liter, and 50 to 75 nmol per liter in 2.6%, 22.0%, and 40.9% of participants, respectively.[18] A severe or moderate deficiency was more prevalent among women and non-Hispanic Black Americans; during winter, when ultraviolet B radiation is insufficient to synthesize the vitamin in skin at northern latitudes; and among persons 20 to 29 years of age. Behaviors that screened out sunlight and low milk intake also predicted a severe deficiency. The only good dietary sources of vitamin D are oily fish, eggs, and fortified foods, including dairy products and breakfast cereals.

There is still debate about the cutoff values for serum concentrations of the vitamin D biomarker (25-hydroxyvitamin D), but the National Academy of Medicine (known as the Institute of Medicine before 2015), National Osteoporosis Foundation, and American Geriatrics Society specify a level of less than 30 nmol per liter as deficiency.[19] For most people, a level of 50 nmol per liter is adequate, although the Endocrine Society recommends a level of 75 nmol per liter to maximize the benefits for bone and muscle. The National Academy of Medicine recommends an intake of 600 IU of vitamin D per day for persons 1 to 70 years of age and 800 IU per day for those who are 71 years of age or older.[20]

When health outcomes were compared for 25,000 people in the United States who took 2000 IU of vitamin D per day or placebo for 5 years, vitamin D supplementation did not help prevent cancer, heart disease, or depression or, surprisingly, preserve bone mineral density or prevent fractures.[21] However, an updated meta-analysis suggests that vitamin D supplementation reduced total mortality from cancer by 25% in analyses that excluded the first 2 years of follow-up.[22] These and other clinical outcome studies have been summarized by the Office of Dietary Supplements.[19] Evidence that vitamin D supplementation has potential benefits for diabetes, autoimmune disease, and cognitive function is under investigation.

Up to 4000 IU of vitamin D per day is safe for adults, but a higher dose is associated with an increased risk of kidney stones, weakness, and gastrointestinal problems. Vitamin D_3 supplementation leads to greater and more sustained in-

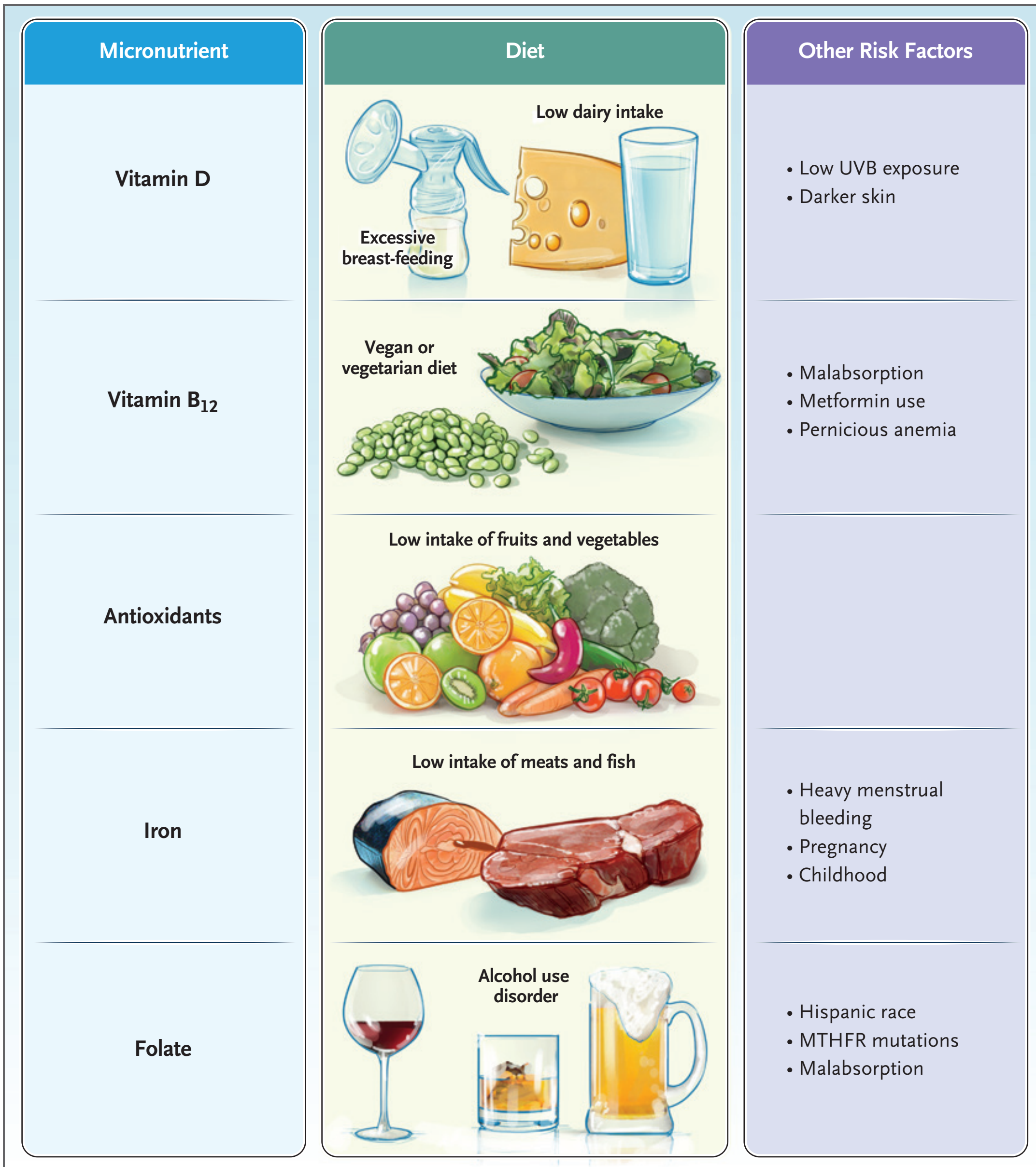

Figure 1. Risk Factors for Micronutrient Deficiencies of Concern in the United States.
MTHFR denotes methylenetetrahydrofolate reductase, and UVB ultraviolet B.

creases in serum 25-hydroxyvitamin vitamin D levels than does vitamin D_2 supplementation, but both forms of vitamin D are effective. Breast milk is low in vitamin D, and the American Academy of Pediatrics recommends that infants under the age of 12 months receive 400 IU of vitamin D per day, but the rate of adherence to this advice is 27%.[23]

VITAMIN B_{12}

Since vitamin B_{12} is found only in animal-source foods, including milk, eggs, and fish, persons who practice the strictest type of vegetarianism — veganism — need to take supplements or consume vitamin B_{12}–fortified foods such as fortified cereals. An inquiry about usual intake of these foods should be a priority if low serum cobalamin concentrations are reported. Persons who consume a vegan diet are not the only ones at risk for vitamin B_{12} deficiency; serum cobalamin levels can also be low in persons who consume a lacto-ovo vegetarian diet (which includes eggs and dairy products), and low levels are common in low- and middle-income countries where intake of animal-source foods is limited.[24,25] Consequences of maternal vitamin B_{12} depletion include poor fetal storage of vitamin B_{12} and low concentrations in breast milk,[26] conditions that result in serious, potentially permanent developmental delays in infants.[27] Older adults, who have an increased prevalence of vitamin B_{12} deficiency, may absorb the vitamin more easily from supplements and fortified grains than from regular foods because of reduced production of gastric acid, which is needed to release the vitamin from foods. The risk of vitamin B_{12} deficiency is increased in persons with malabsorptive conditions and those who have undergone gastric bypass surgery.[28,29]

The active absorption of vitamin B_{12} decreases from approximately 50% of the usual dietary intake of 4 to 6 μg per day to less than 1% at intakes above approximately 25 μg per day from supplements. Nevertheless, the passive absorption of 1% of intakes from high doses of vitamin B_{12} (500 to 1000 μg per day) can improve status over time in persons with the autoimmune disease pernicious anemia who lack the gastric intrinsic factor required for active absorption of the vitamin. Thus, in some cases, repeated intramuscular injections, which are the best strategy for rapid repletion, can be replaced by daily high doses plus serum monitoring to ensure adequacy.[30] The benefits of vitamin B_{12} supplementation for preventing cognitive decline in older adults remain controversial.[31]

IRON

Anemia, defined as a low hemoglobin concentration, is caused primarily by iron deficiency in the United States, where the prevalence of iron deficiency in late pregnancy can reach 30%. The serum ferritin level is an indicator of iron stores and can be used to detect poor iron status before there are hematologic changes. A recent analysis of NHANES data from female participants 12 to 21 years of age revealed iron deficiency in 38.6% of this subgroup when the ferritin cutoff value was 15 μg per liter and in 77.5% when the cutoff value was 50 μg per liter.[32] Iron deficiency anemia affected only 6.3% of the participants in this age group. The main causal factors are heavy menstrual losses, higher iron requirements during pregnancy and early childhood, and diets that are low in the well-absorbed heme iron from animal-source foods. Ferrous iron is the most bioavailable form in supplements, which usually provide 18 mg of iron per day for women.[33] Supplementation with 45 mg or more of iron per day increases the risk of constipation and nausea.

Maternal iron status in pregnancy affects infant iron stores at birth, and poor iron status is a risk factor for low birth weight. Delayed cord clamping is an effective way of increasing iron delivery to newborn infants. The American Academy of Pediatrics recommends an oral iron supplement at a dose of 1 mg per kilogram of body weight until complementary foods containing iron, including iron-fortified cereals, are consumed.

In low- and middle-income countries, only 50% of cases of anemia are due to iron deficiency, with malaria, parasites, and hemoglobinopathies as other causal factors. Micronutrient deficiencies, including vitamin A, vitamin B_{12}, and folate deficiencies contribute relatively little to the global anemia burden. Thus, the high prevalence of anemia in low- and middle-income countries is both relatively intractable and poorly understood. A practical approach to improving the assessment of anemia has been proposed recently.[34]

FOLATE

In the United States, folic acid fortification of cereals, which has been mandatory for wheat flour and rice since 1998 and voluntary for corn masa flour since 2016, has substantially reduced the occurrence of neural-tube defects.[35] The prevalence of folate deficiency is now very low. The upper level for folic acid, the form of folate in supplements and fortified foods, is 1000 μg per day and reflects the concern that higher intake of folic acid might impair vitamin B_{12} status.

ANTIOXIDANTS

Antioxidants (vitamins C and E) have been tested in randomized, controlled trials for their benefits in reducing the risk of cancer, heart disease, and other chronic illnesses, but no such benefits have been found.[36] In fact, clinical trials have shown that high doses of vitamin A (an indirect antioxidant) increase the risk of hip fracture and prostate cancer, and there are adverse effects of vitamin E, including respiratory infections, prostate cancer, and death. However, the use of supplements containing a combination of vitamins C and E, zinc, copper, lutein, and zeaxanthin has been shown to slow the rate of vision loss among patients with age-related macular degeneration.[37]

MICRONUTRIENT RESEARCH AND PROGRAMS IN LOW- AND MIDDLE-INCOME POPULATIONS

In the 1980s, interventions to treat and prevent deficiencies in iodine, vitamin A, and iron were the focus of the international nutrition community. Iodine deficiency was renamed "iodine deficiency disorders" when it became apparent that a range of functions were affected by even a marginal deficiency. In the mid-1980s, randomized, controlled trials conducted in developing countries revealed that supplementation with vitamin A in preschoolers reduced mortality by 34%.[38] On the basis of such observations and increasing awareness of the high prevalence of micronutrient deficiencies, there has been a massive global movement in recent decades to deliver micronutrients through public health programs. The main options are supplementation in the form of tablets, capsules, liquids, and lipid-based supplements; food fortification; biofortification of crops; and nutrition education. Fortification of industrially milled wheat flour, maize flour, rice, or a combination of these grains is legislated in 94 countries. The Food Fortification Initiative supports this effort with evidence-based decisions and monitoring.[4]

Supplementation is usually the preferred intervention for pregnant women and young children, since supplements are rapidly effective and can be targeted and delivered through the health care system. The World Health Organization (WHO) has long recommended iron–folic acid supplements for pregnant women. However, since micronutrient deficiencies rarely occur in isolation in areas where dietary quality is poor, research has focused on the benefits of multiple-micronutrient supplements, especially for pregnant women, infants, and young children. These supplements often contain 15 micronutrients and can be taken as tablets or combined with varying amounts of protein, energy, and essential fatty acids as, for example, lipid-based nutrient supplements (LNS) in sachets. A systematic review and meta-analysis of 13 trials conducted in low- and middle-income countries evaluated the use of small-quantity LNS (100 to 200 kcal per day) in children 6 to 24 months of age and showed that the relative risk of death was 27% lower in the LNS groups than in the non-LNS groups.[39] An assessment of medium-quantity LNS (250 to 499 kcal per day) in infants who were 6 to 23 months of age showed that these supplements were less effective than small-quantity LNS, probably because of the inability of the infants to consume all of the larger amount of supplement.[40] Multiple-micronutrient supplements for pregnant women in low- and middle-income populations reduce the incidence of low birth weight by 9 to 14% as compared with iron–folic acid but have limited benefit in preventing other adverse outcomes.[41] The WHO has therefore recommended multiple-micronutrient supplements during pregnancy "in the context of rigorous research."[41]

FUTURE OPPORTUNITIES

There is increasing interest in using "omic" analyses to investigate the effects of marginal, nonclinical deficiencies on metabolic and genomic functions. For example, in one study, a multiomic approach with the use of both humans and animal models in controlled trials revealed that glutathione sulfotransferase omega-1 (GSTO1) is the best biomarker for zinc deficiency, but this finding has not been tested in other studies.[42] Vitamin B_{12} supplementation in a population of B_{12}-deficient older adults in Chile increased serum levels of plasmalogens, which constitute 70% of the phospholipids in the myelin sheath and 20% of those in the brain.[43] Metabolomic analysis revealed differences in short-chain fatty acids and glycerophospholipids between study participants with insufficient vitamin D and those with sufficient vitamin D in an Irish population of older adults, and supplementation reduced acylcarnitine concentrations.[44] Iron-deficient infant monkeys had changes in liver, serum, and cerebrospinal fluid metabolites before anemia developed, findings that suggest a potential application for determining the risk of anemia and metabolic problems due to infantile iron deficiency.[45] Multiomics could improve our understanding of the physiological effects of poor riboflavin status and poor thiamine status, which are widespread in populations but have not yet raised much public health concern in the absence of symptoms of severe deficiency. Multiomic analysis of the thousands of stored samples from randomized, controlled trials of single or multiple interventions, especially from low- and middle-income populations, could reveal underlying consequences of micronutrient deficiencies and the benefits of interventions.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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