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Review

Main nutritional deficiencies

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Keywords

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Summary

Nutrition is the source of energy that is required to carry out all the processes of human body. A balanced diet is a combination of both macro- and micronutrients. "Nutritional inadequacy" involves an intake of nutrients that is lower than the estimated average requirement, whereas "nutritional deficiency" consists of severely reduced levels of one or more nutrients, making the body unable to normally perform its functions and thus leading to an increased risk of several diseases like cancer, diabetes, and heart disease. Malnutrition could be caused by environmental factors, like food scarcity, as well as disease conditions, like anorexia nervosa, fasting, swallowing inability, persistent vomiting, impaired digestion, intestinal malabsorption, or other chronic diseases. Nutritional biomarkers – like serum or plasma levels of nutrients such as folate, vitamin C, B vitamins, vitamin D, selenium, copper, zinc – could be used for the evaluation of nutrient intake and dietary exposure. Macronutrients deficiencies could cause kwashiorkor, marasmus, ketosis, growth retardation, wound healing, and increased infection susceptibility, whereas micronutrient – like iron, folate, zinc, iodine, and vitamin A – deficiencies lead to intellectual impairment, poor growth, perinatal complications, degenerative diseases associated with aging and higher morbidity and mortality. Preventing macro- and micronutrient deficiency is crucial and this could be achieved through supplementation and food-based approaches.

Introduction

Nutrition is considered as one of the strongest and most adjustable environmental factors that could be used to reduce the burden of disease during an individual's entire life [1]. Appropriate and balanced nutrient's intake and metabolism provide the substrates for the normal physiological functions of the human body [2]. A balanced human diet is based on both macronutrients (e.g. essential fatty acids, carbohydrates, essential amino acids, etc.), which are the major source of energy, and micronutrients (e.g. vitamins, essential minerals, etc.), which are needed for almost all developmental and metabolic processes [3]. Poor nutrition results in an increased risk of several diseases like cancer, diabetes, and heart disease.

Nutritional requirements change during the course of life. For example, during fetal development, infancy, and childhood, the recommended amount of macro- and micronutrients intake is relatively higher with respect to body size. In older individuals, the requirement of certain nutrients (like vitamin D) increases, while other nutrient requirements considerably decrease (like iron and energy) [4].

Other causes of malnutrition can be diseases like anorexia nervosa, fasting, swallowing inability, persistent vomiting, impaired digestion, intestinal malabsorption, or other chronic diseases. Several formulations of food blends are introduced in the diet in order to overcome malnutrition. Malnutrition could also be caused by bad food choices or insufficient food intake [5-9].

Nutritional diseases can cause nutrients deficiencies or excesses, eating disorders, obesity, chronic diseases like cardiovascular diseases, hypertension, diabetes mellitus, cancer, inherited metabolic disorders, developmental abnormalities, food intolerances and allergies [5]. The most prominent nutritional disorder is chronic undernutrition, which affects over 925 million people around the world. Undernutrition is the condition caused by taking insufficient food to fulfil the energy requirement; its main symptoms include weight loss, muscle wasting, body fat wasting, and failure to thrive [8, 9].

Nutrient inadequacies and deficiencies

"Micronutrient inadequacies" are defined as the intake of nutrients in lesser quantity than the estimated average requirement and are prevalent in the United States and other developed countries. These inadequacies mostly occur when the intake of a nutrient is above the deficiency level but below the recommended dietary intake. Unlike micronutrient deficiencies, which lead to clinically evident symptoms, micronutrient inadequacies might cause hidden symptoms that are quite difficult to be identified [10]. Furthermore, an energy-rich and nutrient-poor diet might lead to "hidden hunger" condition, which is characterized by micronutrient inadequacies despite having sufficient or excessive amount of calories. These micronutrient inadequacies could ultimately cause various chronic diseases like cancer, osteoporosis, and cardiovascular diseases. In addition, subclinical or marginal micronutrient deficiencies have also been associated with impaired immunity, general fatigue, and cognitive deficits [11, 12].

Several factors contribute to marginal or lower nutrient status, such as poor quality or quantity of food, increased dietary requirements, greater metabolic losses, or decreased gastrointestinal digestion and absorption. Thus, the continuous consumption of reduced nutritional quantity, because of loss of appetite, or poor quality, like unbalanced, restrictive, or low-nutrients diets, increases the risk of developing poor nutritional status [13, 14]. Other factors contributing to the increased nutritional deficiencies risk include: 1) decreased capacity of nutrient absorption caused by gastrointestinal disorders like coeliac disease, inflammatory bowel disease, reduced absorption of vitamin B12 among elderly, etc., 2) poor bioavailability of nutrients, such as low zinc and iron absorption from the plant-based diets, and 3) reduced bioconversion, such as lower provitamin A carotenoids bioconversion into vitamin A from the plant-based diets. In addition, various genetic polymorphisms and the use of certain medication could also increase the risk of specific nutrient deficiencies [15-17].

Nutritional biomarkers

Accurately estimating the nutrients intake is considered a major challenge. Several countries lack their own food composition databases; therefore, they have to rely on data obtained from the food composition databases of other countries, like the U.S. Department of Agriculture (USDA) Nutrient Database [18].

Nutritional biomarkers can be used for evaluating nutrient intake and dietary exposure [19]. Serum or plasma levels of nutrients like folate, vitamin C, B vitamins, vitamin D, selenium, copper, zinc are reported in the National Health and Nutrition Examination Survey (NHANES) [20].

For instance, body iron status cannot be accurately evaluated through a single biomarker. Therefore, several different analyses calculating serum iron concentration, transferrin saturation levels, serum ferritin concentrations, transferrin receptor, and total iron-binding capacity, are used to estimate the real iron status of the body. It is important, however, to recognize the limitations of the biomarkers used: in fact, due to the homeostatic regulation of the blood concentration of nutrients, the circulatory levels of nutrients are not good indicators of their body status. Additionally, not all nutrients have available biomarkers, and they can change in response to infections, inflammation, age, or kidney function [1, 10].

Thus, nutritional biomarkers and dietary surveys are the two most commonly used methods for assessing the population's dietary exposure. Each of these has its own limitations and advantages, but combined they could work well to estimate dietary intake and nutritional status [10].

Macronutrients Deficiency

Protein-energy malnutrition (PEM)

Protein-energy malnutrition (PEM) is a condition in which individuals have a very little dietary intake of proteins, energy or both; it is thus prevalent in developing countries because of insufficient dietary intake. The two major diseases linked with this condition are marasmus, which is complete food deprivation with exceptionally limited quantities of protein and energy, and kwashiorkor, which is characterized by extreme protein deficiency [5, 21, 22]. The World Health Organization (WHO) Global Database on Child Growth and Malnutrition (from 1980-1993) has shown that PEM has affected almost one-third of the children around the world, 80% of which are living in Asian countries [2, 23].

Infants with marasmus are exceptionally underweight, as they have lost almost all their subcutaneous fat. Their body, appearing to be a combination of only bones and skin, is extremely weak and they have higher susceptibility to infections. The major cause of this condition is an extremely low calorie diet intake from all the sources, including protein. If not treated properly, marasmus could lead to death because of starvation [5, 21, 23].

Kwashiorkor is a condition that usually appears in children that, after being weaned from breast milk (containing high-protein), are fed carbohydrate-rich diet sources without sufficient protein intake. The main characteristic of kwashiorkor is the swollen belly, caused by the fluid retention (edema), and affected children are mostly weak, wasted, poorly grown, and more susceptible to infectious diseases [5]. Kwashiorkor suppresses the production of insulin, causing a reduced protein synthesis which leads to hypoproteinemia, immunosuppression, edema, and diarrhea [23].

Marasmus-kwashiorkor could also appear in institutionalized or hospitalized patients that get intravenous glucose for long time like during recovery from illness or surgery, or with diseases causing appetite loss or nutritional malabsorption [5].

Carbohydrates deficiency

Specific cells of human body, like neurons, need high amounts of glucose. In the absence of adequate dietary carbohydrates, gluconeogenesis depends upon the breakdown of amino acids that are obtained from dietary proteins, body proteins, and glycerol obtained from fats [21]. Gluconeogenesis mostly takes place in the liver. Long-term insufficiency of carbohydrate intake could lead to a condition called ketosis (increased ketones production), that is characterized by the peculiar sweet odor of the patient's breath. Ketosis and other complications linked with low carbohydrate intake can be prevented by consuming daily 50 to 100 g of carbohydrate; although, for a healthy and balanced diet, at least about half of the daily calorie intake should be obtained from carbohydrates, which means a minimum of 250 g of daily carbohydrate intake. The most common sources of carbohydrates in human diet are fruits, vegetables, whole-grain cereals, and legumes, which also give necessary dietary fibers intake [5, 21].

Essential fatty acids deficiency

Omega-3 and Omega-6 are polyunsaturated and essential fatty acids (EFA). Clinical symptoms of EFAs deficiency include diminished growth in children and infants, scaly dry rash, reduced wound healing, and increased infection susceptibility. Omega- 3, 6 and 9 fatty acids compete for the same fatty acid desaturases. One of the prominent biomarkers for essential fatty acid deficiency is omega-9. Furthermore, among the main indicators of EFA deficiency is the plasma eicosatrienoic acid and arachidonic acid (triene:tetraene) ratio higher than 0.2. This condition has been reported in patients suffering from chronic fat malabsorption and cystic fibrosis [24-26].

Several observational and research studies have reported the association of lower omega-3 index with higher risk of mortality by coronary heart disease. Furthermore, in 2016, a meta-analysis established that the supplementation of omega-3 PUFA during pregnancy decreases the risk of premature births and increases the birth weight and gestational age at delivery. Several preparations of omega-3 fatty acid have been approved and recommended by US Food and Drug Administration for hypertriglyceridemia treatment [24, 27-29]. Similarly, replacing other dietary saturated fatty acids (SFAs) with omega-6 PUFA decreases the total blood cholesterol [24, 30, 31].

Micronutrient deficiencies

Micronutrients are crucial for sustaining life. A lower micronutrient consumption than the current Recommended Dietary Allowance Important might lead to chronic metabolic disorders [3]. The inadequacy of any constituent of the metabolic system directly affects both individuals and societies by causing poorer health, reduced work capacity, decreased educational accomplishment, and lower earning potential [1, 32].

In industrialized and developing countries micronutrient deficiencies affect more than 2 billion people of all ages [21], especially pregnant women and children below 5 years of age [1]. Micronutrient deficiencies are linked with almost 10% of children deaths [5, 22]. Iron, folate, zinc, iodine, and vitamin A are among the most occurring micronutrient deficiencies in the world, and all of these contribute to intellectual impairment, poor growth, perinatal complications, and higher morbidity and mortality [1]. In addition, micronutrient deficiencies accelerate mitochondrial decay and degenerative diseases associated with aging [5].

Preventing micronutrient deficiencies is thus crucial and it can be achieved through supplementation and food-based approaches. Micronutrient deficiencies should be determined through reliable and validated biomarkers [1].

Vitamin A deficiency

Vitamin A deficiency is a relatively frequent nutrient deficiency in developing countries and it primarily causes ophthalmologic diseases. In fact, vitamin A is crucial for preserving the integrity of epithelial tissues in the eye and in the urinary, intestinal, and respiratory tracts. The initial clinical symptoms of vitamin A deficiency include xerophthalmia, Bitot spots development, and night blindness. With the progression of the vitamin A deficiency, keratomalacia and permanent blindness may take place. Furthermore, children with vitamin A deficiency may also exhibit protein energy malnutrition [33].

According to the estimation of the WHO, almost 70-80 million children around the world suffer from subclinical vitamin A deficiency, apparently without clinical symptoms. In subclinical vitamin A deficiency, children have higher infection susceptibility and reduced physical growth [33, 34].

B vitamins deficiencies

Vitamin B6

Vitamin B6 is water-soluble and can be obtained from different foods and supplements. It mainly exists in three forms (pyridoxine, pyridoxamine, and pyridoxal), which are biologically active in their phosphorylated forms. Vitamin B6 acts as a coenzyme for several enzymes, such as those essential for amino acids decarboxylation and transamination, neurotransmitter synthesis, fatty acid metabolism, and tryptophan conversion to niacin. Vitamin B6 deficiency is not very common, but can occur due to insufficient dietary intake, malabsorption, and use of certain medications. Malnourished, elderly, and anorexic individuals are at higher risk of developing vitamin B6 deficiency. Alcoholics are also at higher deficiency risk, since they have poor vitamin B6 dietary intake and alcohol increases its catabolism. Vitamin B6 deficiency causes anemia, peripheral neuropathy, seborrheic dermatitis, glossitis, cheilosis, depression, celiac disease, Crohn disease, and seizures. Medications can bind vitamin B6 and increase its excretion or reduce its enzymatic activity [2].

Vitamin B12

For humans, animal products like dairy and meat are the only dietary source of vitamin B12. Although currently the incidence of vitamin B12 deficiency in the United States is not fully known, the NHANES III (1991-1994) reported a frequency of 1 in 200 children of 4-19 year age with decreased levels of vitamin B12 (< 200 pg/mL). Clinically, vitamin B12 deficiency is uncommon among infants or children without any predisposing factors. In early stages, cobalamin deficiency is secondary to the maternal deficiency among breast-feeding mothers following strict or moderate vegan diets. The main causes of vitamin B12 deficiency mostly are inadequate intake, inborn errors of metabolism or transport, and malabsorption. Elder individuals, people with psychiatric illnesses, vegans, and their breastfed infants are at higher risk of vitamin B12 deficiency because of the insufficient intake [2, 35].

Folate deficiency

Vitamin B9 (folic acid, folate) and Vitamin B12 have several closely linked functions. Folate is crucial for purines and thymidylate synthesis and plays a significant role in DNA synthesis, repair and stability. Folate is also involved in carbon metabolism and changes in DNA methylation pattern. Folic acid deficiency can be caused by excessive consumption of alcohol, since it impairs vitamin absorption. Individuals with folate deficiency exhibit fatigue and weakness caused by megaloblastic anemia. In pregnancy, folate deficiency is linked with preterm delivery, low birth weight, retardation of fetal growth, and neural tube defects. Moreover, folic acid supplementation during the periconceptional period decreases the incidence of neural tube defects [1, 5, 21].

Vitamin C deficiency

Vitamin C (ascorbic acid) is considered an essential nutrient and is mainly derived from diet; its deficiency causes scurvy and could also lead to behavioral and mood changes [2]. In the first 3 months of ascorbic acid deficiency, the symptoms are bleeding gums, petechiae, ecchymoses, hyperkeratosis, coiled hairs, impaired wound healing, and arthralgias [33]. Vitamin C plays a significant role also in osteoblast and osteodentin formation, carnitine synthesis, catecholamines synthesis, reductions of urinary folic acid excretion, and higher dietary iron absorption.

Humans are incapable of synthesizing vitamin C, therefore they totally depends upon dietary vegetables and fruits for its sufficient intake and storage. Good vitamin C sources can be citrus fruits, tomatoes, strawberries, potatoes and green leafy vegetables [2]. Furthermore, vitamin C deficiency is observed in growing infants exclusively fed with cow milk or formula and in children with neurodevelopmental disabilities. Pharmacological doses of vitamin C are known to resolve the symptoms [33, 36].

Vitamin E deficiency

Vitamin E comprises a group of eight fat-soluble compounds, the most important of which is tocopherol. Vitamin E protects against the free radical damage associated with chronic diseases. Vitamin E deficiency-associated disorders are not very common. Vitamin E deficiency can occur in individuals with fat malabsorption or specific genetic disorders, like Friedreich ataxia and abetalipoproteinemia. Research data have shown that vitamin E may prevent diseases like diabetes, atherosclerosis, ischemic heart disease, Alzheimer, cataracts, and Parkinson. Studies have also reported the protective effect of vitamin E against cancer [33, 37].

The major characteristics of vitamin E deficiency include ataxia, myopathy, and pigmented retinopathy, like retinitis pigmentosa with vision loss. At the later stages of vitamin E deficiency, sensory motor neuropathy takes place, with loss of position, vibration sense and reflexes, and generalized weakness [33, 38].

Vitamin K deficiency

Vitamin K deficiency leads to coagulation disorder, which manifests by increased prothrombin time and international normalized ratio, with normal levels of fibrinogen and platelets. In newborns, vitamin K deficiency is called "hemorrhagic disease of the newborn". Early vitamin K deficiency at birth (VKDB), which manifests within the first 24 hours after birth, usually affects infants whose mothers during pregnancy have been taking medications that inhibit vitamin K metabolism. Usually, at-risk infants have 6-12% chances of developing VKDB without being administered vitamin K at birth. Late VKDB, on the other hand, is linked with babies fed only with breast milk and it starts between 8 days to 6 months of age. Usually, the clinical manifestation of late VKDB is quite severe, with a mortality rate ranging between 20 and 50% of infants undergoing intracranial hemorrhage. Infants with malabsorptive syndrome or cholestasis are at higher risk. A single intramuscular dose of vitamin K at birth in wholly breast-fed infants seems to prevent the development of late VKDB, but in order to prevent this condition it is advisable to also repetitively add vitamin K oral administration [33, 39].

Vitamin D deficiency

Vitamin D, also called calciferol, is a fat-soluble secosteroid that is essential for the intestinal absorption and metabolism of calcium, magnesium and phosphorous. Vitamin D stimulates the osteoclasts to release calcium and phosphorus, and activates the synthesis of enterocyte calcium channel, which enhances the absorption of calcium. Vitamin D can be acquired through dietary sources, like ergocalciferol/vitamin D2, or endogenously synthesized, like cholecalciferol/vitamin D3. Vitamin D sources are fish and fish oils (which contain the highest proportion of available vitamin D), eggs, shiitake mushrooms, liver, and fortified foods (like orange juice and milk) [2]. Vitamin D deficiency causes hypocalcemia and hypophosphatemia, which lead to osteomalacia among adults and rickets among children. Furthermore, vitamin D deficiency is associated with immunomodulatory disorders, cardiovascular diseases, hypertension, and insulin resistance in adults [2, 40].

Vitamin D deficiency depends upon various dietary and environmental factors, such as body mass index, sun exposure, and milk ingestion. Usually, vitamin D deficiency occurs due to its malabsorption, decreased synthesis and reduced dietary intake [41]. In several countries, including North America, cow milk, infant formulas, and different cereals are supplemented with vitamin D [33, 42]. Long-term and short-term therapy of vitamin D deficiency mainly involves vitamin D supplementation and implementation of vitamin D- and calcium-rich diets. In order to solve vitamin D deficiency, for most people over 1 year of age it is considered sufficient to supplement 50,000 IU of ergocalciferol for at least eight weeks [2, 43].

Calcium deficiency

Calcium deficiency or hypocalcemia is characterized by low levels of serum calcium. A long-standing calcium deficiency could lead to cataracts, dental changes, brain alterations, osteoporosis, and rickets. Sufficient calcium intake is crucial throughout life to maintain bone health [44]. In several parts of the world, rickets caused by calcium deficiency is still present. A double-blind, randomized controlled study of 123 Nigerian children suffering from rickets showed that the baseline calcium intake of these children was low, almost 200 mg/d. Moreover, these children reacted better to calcium treatment alone or combined with vitamin D rather than vitamin D alone [45, 46]. In addition, certain diseases and specific diets, like vegetarian diets, might cause calcium deficiency. Calcium supplementation is required also in inflammatory bowel disease patients, particularly those administered with corticosteroids/glucocorticoids [33, 47].

Iron deficiency

Iron deficiency is the most prevalent nutritional deficiency, with young children and premenopausal women at the highest risk of iron deficiency [21, 22]. Being iron a major contributor in hemoglobin synthesis, depletion of its reserves leads to microcytic hypochromic anemia, characterized by smaller-size red blood cells containing a smaller amount of hemoglobin than normal red blood cells. Symptoms of anemia include fatigue, apathy, paleness, weakness, breathing difficulty upon exertion, and decreased resistance for cold temperatures [21]. Iron deficiency could affect development, behavior, learning abilities, and growth during childhood. Severe anemia due to iron deficiency may also increase risks of complications during pregnancy and maternal death. Iron deficiency is mostly caused by insufficient dietary iron intake, blood loss during menstruation, intestinal blood loss, or blood loss due to hookworm, tumors, hemorrhoids, and regular use of drugs like aspirin [5, 21, 22, 48, 49].

Iodine deficiency

Iodine is a trace element that plays a major role in thyroid hormone synthesis. Thyroid hormone is essential for regulating human development and growth. Iodine is naturally present in some foods and is also used as a dietary supplement, added to salt, or used in organic form. Physiologically, iodine reserves are estimated to be 60 µg; on the other hand, during deficiency, the reserves are as low as 10-20 µg [50]. Absorption and utilization of iodine can be impaired due to goitrogens presence or exposure to disulfides, thiocyanates, and percolate [51]. Reduced dietary intakes of iodine (10-20 µg daily) may result in hypothyroidism, followed by goiter. Thyroid hormone is necessary for optimum fetal and postnatal development and growth of the central nervous system [52, 53]. During the early stages of pregnancy, maternal iodine deficiency may lead to iodine deficiency disorder, which causes permanent neurological damage and mental retardation in the offspring [53]. From the embryonic stage to adulthood, iodine deficiency disorder includes diminished mental functions, goiters, cretinism, and hyper- or hypothyroidism. Infants and pregnant women are at the highest risk of developing iodine deficiency [1]. Universally, salt iodization is the most efficient and practical strategy used to reduce global iodine deficiency [1, 54].

Zinc deficiency

Zinc is a trace mineral that is essential for health and is associated with cellular metabolism. Zinc is needed for the proper functioning of over 200 enzymes and is crucial for normal growth and development, immune system function, DNA and protein synthesis, and cell division [55]. Since human body cannot store zinc for long, constant dietary intake of zinc is required to maintain normal functions. Primarily, zinc is found in seafood, animal products, and human breast milk. Zinc absorption is greatly impaired by lignins, phytates and fiber, which reduce the bioavailability of zinc from non-animal sources [1, 56]. Severe zinc deficiency has been reported in patients fed with intravenous solutions lacking zinc and in people suffering from hereditary zinc metabolic disorders like acrodermatitis enteropathica. Zinc deficiency symptoms can include skin lesions, increased susceptibility to infection, diarrhea, poor appetite, night blindness, reduced taste and smell acuity, hair loss, low sperm count, impotence, and slow wound healing [5, 22]. In the developing countries, zinc deficiency is considered one of the main causes of morbidity [57]. Furthermore, zinc supplementation during pregnancy is linked with a substantial decrease in the number of preterm births without affecting the infants' birth weight [58, 59].

Magnesium deficiency

In humans, magnesium deficiency is linked with colorectal cancer, osteoporosis, hypertension, metabolic syndrome, and diabetes. In human primary cell cultures, magnesium deficiency results in mitochondrial DNA damage, increased telomere shortening, activation of cell-cycle arrest proteins, and premature senescence. Common magnesium sources include beans, green leafy vegetables, nuts and whole grains. In rats, magnesium deficiency can cause chromosome breakage and cancer [3, 60, 61]. Magnesium blood levels are strongly controlled and therefore could not be used for the assessment of the nutritional status of magnesium [62, 63].

Selenium deficiency

Selenium is an essential trace mineral that is mostly found in certain foods, soil and water. Selenium acts as a cofactor of many enzymatic reactions, also playing role in redox function, production of active thyroid hormone, and immune function. Selenium also constitutes selenoproteins such as glutathione peroxidase, thioredoxin reductase, and selenoprotein-P. Nutritional selenium deficiency happens in regions with reduced selenium content in soil. Serious selenium deficiency could lead to Keshan disease, an endemic cardiomyopathy, and Kashin-Bek disease, a deforming arthritis. Moreover, selenium deficiency has a negative impact on spermatogenesis, immunocompetency, thyroid function, cardiovascular diseases, and mood swings [32, 64].

Potassium deficiency

According to US Dietary Guidelines 2015 to 2020, potassium is considered as a nutrient of public health concern, since it is not sufficiently consumed by the US population. Furthermore, US national surveys have reported that the majority of American population do not take the recommended amount of potassium. NHANES survey 2011-2012, concerning 4,730 subjects, has revealed that less than 3% of US adults had a potassium intake over the required amount, 4,700 mg/day [44]. The main potassium sources include vegetables and fruits [65].

Fluoride deficiency

Fluoride plays a significant role in the mineralization of teeth and bones and protects them from tooth decay. Several US epidemiological studies (1930s to 1940s) have reported an inverse relationship of the amount of natural fluoride in water with dental caries rate. Areas with low fluoride levels in drinking water are prescribed to add fluoride supplements for children over 6 months of age; in those regions dentists recommend fluoride rinses or gels to be periodically applied to their patients' teeth. Fluoridated toothpastes are significant fluoride source for both children and adults, providing a continuous fluoride intake [5, 21, 22]. Antacids containing aluminum could decrease fluoride absorption. Therefore, it is recommended to take these antacids two hours before or after fluoride supplementation [66].

Biotin

Biotin is an essential cofactor of four carboxylases: pyruvate carboxylase, acetyl-CoA carboxylase, 3-methylcrotonyl-CoA-carboxylase, and propionyl-CoA-carboxylase. Biotin is both synthesized by the intestinal bacteria and obtained from dietary sources. Sources of dietary biotin are eggs, walnuts, liver, mushrooms, peanuts, soybeans, and cow milk. Since biotin is both available from dietary sources and synthesized by the human microbiota, acquired biotin deficiency is very rare. Most of the acquired biotin deficiencies are linked with excessive intake of raw egg whites, gastrointestinal malabsorption, extended parenteral nutrition, and extended use of anticonvulsants. Biotinidase deficiency leads to metabolic acidosis, conjunctivitis, ataxia, organic aciduria, developmental delay, encephalopathy, sensorineural hearing loss, seizures, periorificial dermatitis, and alopecia [2, 67].

Causes of micronutrient deficiencies

Micronutrient deficiencies can be caused by either insufficient intake or impaired absorption, which ca be due to infections or chronic inflammation. In infants, micronutrient deficiencies are caused by maternal micronutrient deficiencies in utero or due to rapid postnatal growth [1, 68, 69].

Low- or middle-income countries have the highest micronutrient deficiencies burden; however, some micronutrient deficiencies can also exist in certain subpopulations of high-income countries [1]. Lactation and pregnancy also increases the requirements of macro- and micronutrients. An inadequate nutritional intake of pregnant mothers may lead to insufficient nutritional levels in infants and children, thus causing stunting, infection susceptibility, and developmental delays [70, 71]. Nutrient deficiency can also be caused by selective diets: any diet that completely excludes a specific food group is potentially inadequate for macro- and micronutrient intake. For example, vegan diets exclude all animal-based foods, thus leading to an increased risk of causing B vitamins deficiency. Similarly, various energy-limiting diets used for weight loss may cause an increased micronutrient deficiency risk [66, 72]. Chronic alcoholism causes depletion of the liver reserves of vitamin A and might contribute to alcohol-induced cirrhosis [66, 73]. To break the malnutrition cycle, it is critical to make an intervention during the first malnutrition 1,000 days; however, a well-coordinated and sustainable commitment is required to increase the global nutrition levels. To achieve this goal, it is critical to better understand the epidemiology of micronutrients deficiencies and to select the best-suited interventional strategies [1].

Nutrient deficiency screening test

An important requirement for screening individuals that are at risk of specific nutrient deficiency or inadequacy is the availability of an accurate and suitable test, with sufficient specificity and sensitivity. In order to determine the nutritional status of the majority of minerals and vitamins, blood, saliva, and urine-based biomarkers are available, using nominally invasive sampling. These biomarkers can detect particular nutrient deficiencies at an early stage, before symptoms development. Thanks to technology advancement, sensitive methodologies are being developed that measure the nutritional status of omega-3 polyunsaturated fatty acid by simple blood draw, whereas in some countries only finger-prick blood tests are available [74].

Several advanced screening tools and techniques have been established for the identification of patients or elderly at risk of protein or calorie malnutrition. Some of the biomarkers that reveal general malnutrition include body mass index, total cholesterol, and hemoglobin. Another approach to evaluate the risk of certain nutrients insufficient intake is using validated dietary questionnaires. However, usually these dietary questionnaires are time-consuming and not sensitive enough [75].

Importance of dietary supplements

Mineral and vitamin supplements are the most frequently used kinds of dietary supplementation worldwide. [76] National Health and Nutrition Examination Survey

(NHANES) data revealed that, despite their micronutrient intake from all sources (like enriched and fortified foods), almost 90% of the US adult population takes less than the estimated average requirement for vitamins D and E, 51% for vitamin A, 43% for vitamin C, 61% for magnesium, and 49% for calcium. Besides, only 39% and 2% of the adult US population had respectively potassium and vitamin K intakes over the recommended adequate intake. Low micronutrients intake is also prevalent in children of 2 to 18 years of age, particularly for minerals like magnesium and calcium, and for vitamins D, E and K [77, 78].
Usage of multivitamin/multimineral supplements is frequent in the USA. Data from NHANES 2011 to 2012 establish that almost 31% of adults from USA take multi-vitamin/multi-mineral supplements because they contain at least 10 micronutrients [79]. Generally, dietary supplements usage is more common in non-Hispanic whites, females, elderly people, and educated individuals [80]. Several research studies have reported that using multi-vitamin/multi-mineral supplements is linked with greater micronutrient intake, thus suggesting they could help filling nutritional gaps and improving the nutrient adequacy among populations. In comparison with the micronutrient intake from food source alone, using multi-vitamin/multi-mineral supplements is also associated with decreased prevalence of several "shortfall" nutrients inadequacies, such as iron, magnesium, calcium and vitamins A, C, D and E (NHANES 2009-2012) [81]. Afshin et al. in their research study established that diet improvement could potentially prevent one fifth of deaths worldwide [80]. Furthermore, the American Academy of Pediatrics proposed that all adults, infants, and children should take 400 IU of vitamin D supplementation, 400 µg/day of vitamin B supplementation and 400 mg of vitamin C supplementation daily [77, 82].

Conclusion

Nutritional deficiencies not only cause developmental failure, loss of various body functions, and several other diseases such as diabetes, vision loss, immunity loss, and cancer, but it also has several long-term effects on economic productivity. The major causes of nutritional deficiencies are insufficient intake of food, inability to absorb nutrients, and consumption of diets that lack some of the essential nutrients. Micronutrient deficiencies are the most prevalent type of nutritional deficiencies, usually caused by the insufficient intake of one or more of the micronutrients that are essential to maintain optimal health. Some of these essential micronutrients are iron, iodine, calcium, zinc, magnesium, fluoride, and vitamins A, B6, B12, C, D, E and K. Macro- and micronutrient deficiencies may cause several serious diseases, like goiter, mental retardation, acute respiratory infections, decreased cognitive function, cancer, vision loss, rickets, pellagra, beriberi, and diarrhea. Dietary supplementation is one of the major solutions for managing micronutrient deficiencies, as it can increase the under-consumed nutrients intake within a population and fill the nutritional gaps.

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Conflicts of interest statement

Authors declare no conflict of interest.

Author's contributions

MB: study conception, editing and critical revision of the manuscript; AKK, Kristjana D, Kevin D, BA, VV, GM, AI, STC, FB, PG: literature search, editing and critical revision of the manuscript. All authors have read and approved the final manuscript.

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