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Health Benefits of Micronutrients (Vitamins and Minerals) and their Associated Deficiency Diseases: A Systematic Review

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Abstract

The research focused on the benefits of micronutrients (vitamins and minerals) and their associated deficiency diseases and health complications. Micronutrients are essential elements required by human and other organisms in varying quantities throughout life to coordinate a range of physiological functions for health maintenance. For human nutrition, micronutrients are required in amounts generally below 100 milligrams per day, while macronutrients are required in gram amounts daily. Vitamins and minerals are essential micronutrients. Essential nutrients cannot be synthesized in humans, either at all or may be in insufficient amounts, and therefore must be obtained by the diet. Vitamin C can be synthesized by some organisms but not by others; it is not a vitamin in the first instance but is in the second. In humans there are 13 vitamins: 9 water-soluble (8 B vitamins and vitamin C) and 4 fat-soluble (A, D, E, and K). Vitamins A and D can amass in the body, which may result in dangerous hypervitaminosis. Anti-vitamins inhibit the actions or absorption of vitamins; avidin inhibits biotin absorption, although it is deactivated by cooking; Pyrithiamine inhibits enzymes that use vitamin B_1. The four key structural elements in human body (oxygen, hydrogen, carbon, and nitrogen) by weight, are often not included in the lists of major nutrient minerals (nitrogen is a "mineral" for plants, as it is often included in fertilizers). These four key elements compose around 96% of the weight of human body, and the major minerals (macrominerals) and minor minerals (trace elements) compose the remaining percent. The five major minerals in the the human body are calcium, phosphorus, potassium, sodium, and magnesium (macrominerals or macroelements). The trace elements with specific biochemical function in human body are iodine, sulfur, zinc, iron, chlorine, cobalt, copper, manganese, molybdenum, and selenium. Calcium makes up 920 to 1200 g of body weight (about 1.5% of body weight) of an adult, with 99% of it contained in the bones and teeth. Phosphorus occurs in amounts of around 2/3 of calcium, and makes up approximately 1% of an individual's body weight. The

other macroelements (potassium, sodium, magnesium, chlorine, and sulfur) make up only around 0.85% of the body weight.

Key words: *Micronutrients, Vitamins, Minerals, Vitamins deficiency diseases, Minerals deficiency diseases*

1.0 INTRODUCTION

Micronutrients (vitamins and minerals) have numerous health benefits including tissue maintenance, bone and teeth formation and health, serving as cofactors and coenzymes to enzyme various enzyme systems, aiding the regulation and coordination of most body functions, and other biochemical and physiological functions in the body. Micronutrients are essentially required by human and other organisms in varying amounts throughout life to coordinate various physiological functions to maintain health (Gernand *et al.*, 2016; Tucker, 2016). Humans and other animals require several vitamins and minerals (Blancquaert *et al.,* 2017). Micronutrient requirements in humans are in amounts generally below 100 mg/day, in contrast to macronutrients which are required in grams per day. The minerals for human and animals include 13 elements such as calcium and iron which originate from the Earth's soil and cannot be synthesized by living organisms (Corvallis, 2018; USDA, 2016). Micronutrient requirements for humans also include vitamins, which are organic compounds required in micrograms or milligrams (USDA, 2016; Corvallis, 2018). Since plants are the main origin of nutrients for humans and other animals, some micronutrients can be in low quantities and deficiencies can occur when there is insufficient dietary intake, as occurs in malnutrition, indicating the need for initiatives to prevent inadequate supply of micronutrient in plant foods (Blancquaert *et al.*, 2017), including the combinations of foods and flours to ensure nutrient complementation (Awuchi *et al*., 2019; Awuchi, 2019b), as commonly practiced in food industries.

Multiple micronutrient powder of at least vitamin A, iron, and zinc was added to the WHO's List of Essential Medicines in 2019 (WHO, 2019). At 1990 World Summit for the Children, the gathered countries identified deficiencies in 2 microminerals and 1 micronutrient (iron, iodine, and vitamin A) as being predominantly common and posing risks to public health in developing countries (UNICEF, 1998). The Summit set goals for eliminating these deficiencies. The Micronutrient Initiative based in Ottawa was formed in response to the challenge with the mission to carry out research and implement and fund micronutrient programming.

Minerals are required as essential nutrients by organisms including human to carry out the functions required for life and health. As programming around these micronutrients increased, new research in 1990s led to implementation of zinc and folate supplementation programmes as well. The priority programs include vitamin A supplementation for children 6 to 59 months, supplementation of iron and folate for women of child-bearing age, supplementation of zinc as a treatment for diarrhoeal diseases, staple food fortification, salt iodization, multiple micronutrient powders, behavior-centered nutrition education, and bio-fortification of crops.

Salt iodization is the recommended approach for ensuring adequate iodine intake by human both in developed and developing world. To iodize salt, some level of potassium iodate is added to salt after refining and drying and before packaging. Although large-scale iodization of salt is most efficient, with the proliferation of small-scale manufacturers of salt in developing nations, technology for small-scale iodization of salt has also been developed. The international organizations work with the national governments to identify and support small scale salt manufacturers in adopting iodization. In 1990, less than 20% of households in developing nations were consuming iodized salt. By the year 1994, international partnerships had formed global campaign for the Universal Salt Iodization. By the year 2008, it was estimated that 72% of households in developing nations were consuming iodized salt (UNICEF, 2010) and the number of the countries where iodine deficiency disorders were public health concern decreased from 110 to 47 countries; more than half.

In 1997, national programming of vitamin A supplementation received a boost when experts came together to discuss quick scale-up of supplementation activities and the Micronutrient Initiative, given the support from the Canada Government, started to ensure the supply of vitamin A to UNICEF. In areas with deficiency of vitamin A, it is recommended that children aged 6 to 59 months receive 2 doses annually. In many nations, vitamin A supplementation often is combined with campaign-style health events and immunization. Global efforts for vitamin A supplementation have targeted 103 priority nations. In 1999, 16% of children in these nations received 2 doses of vitamin A annually. By the year 2007, the rate increased to 62%. The Micronutrient Initiative, with the funding from the Canada Government, supplies 75% of the required for supplementation of vitamin A in developing countries.

The Double-fortified salt (DFS) is public health tool for the delivering of nutritional iron. DFS is fortified with both iron and iodine. DFS was developed by Venkatesh Mannar, the Executive Director of Micronutrient Initiative and the University of Toronto Professor Levente L. Diosady, who discovered a process for the coating of iron particles with vegetable fat to prevent negative interaction of iodine and iron (Levente *et al.,* 2019).

Tata Salt Plus, in India, priced at economical rate of Rs 20 per kg, is iodine plus iron fortified salt, made by National Institute of Nutrition, Hyderabad by double fortification technology. The double fortification technology was offered to the Tata Chemicals under long-term MoU after proper studies on bio-availability across population strata done and published by the National Institute of Nutrition. It was first used in 2004 in public programming. In September 2010 DFS was produced in Indian State of Tamil Nadu and distributed by a state school feeding program. Double-fortified salt has also been used to fight Iron Deficiency Anemia (IDA) in Indian state of Bihar. In the same September 2010, Venkatesh Mannar was named Laureat of the California-based Technology Awards for his work in developing DFS.

Micronutrients are essential for healthy living, and should augmented with proper hygiene, including adequate body management and waste disposal (Awuchi and Igwe, 2017). Micronutrient requirements are in amounts generally below100 mg/day, while macronutrients are required in grams per day. Micronutrient requirements for human also include vitamins; organic compounds required in microgram (µm) or milligram (mg) amounts. Micronutrient deficiency is not sufficient amount of one or more of micronutrients required for optimal health. In humans and in other animals they include both deficiencies of vitamins and minerals.

2.0 VITAMIN

Vitamins are organic compounds (or related set of molecules) which are essential micronutrients that organisms including humans require in minute quantities, usually within micrograms (millionths of a gram) to milligrams (thousandths of a gram), for proper functioning of their metabolism. Essential nutrients cannot be made or synthesized in the human body (organism), either at all or in insufficient amounts, and therefore must be obtained by the diet, just as some beneficial phytochemicals are not synthesized in the body (Awuchi, 2019a). Vitamin C can be synthesized by a few species but not by others; in the first instance, it is not a vitamin, but is in the second instance. The term *vitamin* does not cover the three other groups of the essential nutrients: minerals, essential amino acids, and essential fatty acids (Maton *et al.,* 1993). Most vitamins are not single molecules, rather they are groups of related molecules known as vitamers. For instance, vitamin E comprises of four tocopherols and four tocotrienols. Thirteen vitamins required by human metabolic functions are: vitamin A (as all-*trans*-retinyl-esters, all-*trans*-retinol, and all-*trans*-beta-carotene as well as other provitamin A carotenoids), thiamine (vitamin B_1), riboflavin (vitamin B_2), niacin (vitamin B_3), pantothenic acid (vitamin B_5), pyridoxine (vitamin B_6), biotin (vitamin B_7), folic acid or folate (vitamin B_9), cobalamins (vitamin B_{12}), ascorbic acid (vitamin C), calciferols (vitamin D), tocopherols and tocotrienols (vitamin E), and quinones (vitamin K).

Vitamins have various biochemical functions. Vitamin A functions as regulator of cells and tissue growth and differentiation. The B vitamins function as enzyme cofactors and coenzymes or their precursors. Vitamin D provides hormone-like functions, regulating mineral metabolism for the bones and other organs in the body. Vitamins C and E act as antioxidants (Bender, 2003), preventing cells oxidation by free radicals in the body. Both deficient and excessive intake of vitamins can potentially result in clinically significant illness, though excessive intake of water-soluble vitamins is unlikely to do so.

Prior to 1935, the food was the only source of vitamins. If intake of vitamins was lacking or deficient, the result was deficiency of vitamins and consequent deficiency diseases. At that moment, commercially manufactured tablets of yeast-extract B complex vitamins and the semi-synthetic vitamin C became available. It was followed in 1950s by mass production and marketing of the supplements of vitamins, including multivitamins, to prevent the deficiencies of vitamins in the general population. The governments mandated the addition of vitamins to staple diets such as milk or flour, known as food fortification, to prevent the deficiencies. The recommendations for folic acid (folate) supplementation during pregnancy decreased risks of infant neural tube defects (Wilson *et al.,* 2015). Although reducing the incidence of deficiencies of vitamins clearly has benefits, the supplementation is believed to be of small value for healthy individuals who are consuming vitamin-adequate diets (Fortmann *et al.,* 2013).

The word *vitamin* was first derived from the term *vitamine*, coined by Polish biochemist Casimir Funk in 1912, who isolated complex of micronutrients essential to life, which he presumed to be amines. After this presumption was later determined to be untrue, the "e" was removed from the name (Combs, 2007). All vitamins were discovered or identified within 1913 and 1948.

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2.1 Classification of vitamins

Vitamins are classified as either fat-soluble or water-soluble. In humans there are 4 fat-soluble (A, D, E, K) and 9 water-soluble (vitamin C and 8 B vitamins), making them 13 vitamins. Water-soluble vitamins easily dissolve in water and, generally, are excreted readily from the body, to the extent that urinary output is strong predictor of vitamin consumption (Fukuwatari and Shibata, 2008). As they are not as stored readily, more continuous intake is important. The fat-soluble vitamins are absorbed via the intestinal tract with help of lipids (fats). The vitamins A and D can accrue in the body, which may result in dangerous hypervitaminosis (excess vitamins). Fat-soluble vitamin deficiency as a result of malabsorption is of most significance in cystic fibrosis (Maqbool and Stallings 2008).

2.2 Anti-vitamins

Anti-vitamins are biochemical or chemical compounds which inhibit the actions or absorption of vitamins. For example, pyrithiamine, a synthetic compound, has molecular structure similar to vitamin B_1 (thiamine) and inhibits the enzymes that use vitamin B_1. Avidin, a protein in raw egg whites, inhibits the absorption of biotin; it is easily deactivated by heat treatment such as cooking.

2.3 Biochemical functions of vitamins

Every vitamin is typically used in multiple biochemical reactions, and as a result have multiple functions.

2.3.1 Fetal growth and childhood development

Vitamins are essential for growth and development of multicellular organisms, including humans. Using genetic blueprint inherited from parents, a fetus develops from nutrients it absorbs. It requires the presence of some vitamins and minerals at certain times (Wilson *et al.*, 2015). These nutrients facilitate the biochemical reactions that produce skin, bone, and muscle, among other things. If there is severe deficiency in at least one of these nutrients, a child can develop deficiency disease. Even minor deficiencies can cause permanent damage (Gavrilov, 2003).

2.3.2 Adult health maintenance

As soon as growth and development are completed, the vitamins remain essential nutrients for healthy maintenance of cells, organs, and tissues that make up multicellular organisms; they also enable multicellular life form to efficiently and sufficiently use the chemical energy provided by diets, and to help process the proteins, carbohydrates (sugars, starch, etc.), and fats required for the cellular respiration (Bender, 2003); sugar alcohols such as sorbitol, xylitol, etc. used as sugar substitutes in most beverages provide very little or no energy to the body (Awuchi and Echeta, 2019; Awuchi, 2017). The main sources of energy remain carbohydrates, fats, and, sometimes, proteins.

2.4 Vitamins intake

2.4.1 Sources

For the most part, the vitamins are obtained from the food, but some are acquired through other means: for example, the microorganisms in the gut flora make biotin and vitamin K; and a form of vitamin D is synthesized in the skin cells when they are exposed to some wavelength of UV light present in the sunlight. Humans can make some vitamins from precursors they eat: for example, the vitamin A is synthesized from the beta carotene; and niacin is synthesized from tryptophan, an amino acid (Institute of Medicine, 1998). The Food Fortification Initiative (FFI) lists countries which have compulsory fortification programs for vitamins niacin, vitamin A, folic acid, and vitamins B1, B2 as well as B12.

2.4.2 Deficient intake of vitamins

The body's stores for different vitamins widely vary; vitamins B_{12} A, and D are stored in significant amounts, mostly in the liver, and adult's diet might be deficient in vitamins D and A for many months and vitamin B_{12} in certain cases for years, before developing deficiency condition. However, vitamin B_3 (i.e., niacin and niacinamide) does not store in significant amounts, so the stores may last only a few weeks. For vitamin C, the first scurvy symptoms in experimental studies of thorough vitamin C deprivation in humans have widely varied, from one month to above six months, depending on the previous dietary history which determined body stores (Pemberton, 2006).

Deficiencies of vitamins are classified into two; either primary or secondary. Primary deficiency occurs when human/organism does not get sufficient vitamin in from food. Secondary deficiency may be as a result of an underlying disorder which limits or prevents the absorption or use of vitamin, due to lifestyle factors, such as excessive alcohol consumption, smoking, or use of medications that interfere with absorption or use of vitamins. People who eat varied diet are not likely to develop severe primary deficiency of vitamins, but may be consuming below the recommended quantities; a national food and supplement survey done in the United States over 2003 to 2006 reported that at least 90% of people who did not consume the supplements of vitamins were found to have inadequate amounts of some essential vitamins, especially vitamins D and E (Bailey *et al.*, 2012).

Well-researched human deficiencies of vitamins involve niacin (pellagra), thiamine (beriberi) (Wendt, 2015), vitamin C (scurvy), vitamin D (rickets), and folate (neural tube defects) (Price, 2015). In much of the developed countries these deficiencies are rare because of an adequate food supply and the vitamins addition to common foods. Along with these classical vitamin deficiency diseases, a number of evidence has also linked vitamin deficiency to many different disorders (Lakhan and Vieira, 2008; Boy *et al.*, 2009).

2.4.3 Excess intake of vitamins (hypervitaminosis)

Some vitamins have documented chronic or acute toxicity at excess intakes, which is known as hypertoxicity. The European Union and governments of many countries have published Tolerable upper intake levels (ULs) for the vitamins which have documented toxicity (European Food Safety Authority, 2006; National Institute of Health and Nutrition, Japan, 2010). The possibility of eating too much of any vitamin from only food is remote, but excess intakes (vitamin poisoning) from the dietary supplements do occur. In 2016, overdose exposures to all vitamins formulations and multi-vitamin/mineral formulations were reported by 63,931 people to American Association of Poison Control Centers (AAPCC) with 72% of the exposures in children below the age of five (Gummin *et al.*, 2017). In the United States, analysis of national diet and supplement survey

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showed that about 7% of adult vitamin supplement users exceeded the UL for folic acid and 5% of people older than 50 years exceeded UL for vitamin A (Bailey *et al.*, 2012).

2.5 Effects of cooking on vitamins

The USDA has conducted widespread studies on percentage losses of numerous nutrients from different types of food and cooking methods (USDA, 2007). Some vitamins might become more bio-available (usable by the body) when food is cooked. The table below shows the numerous vitamins that are susceptible to loss due to heating—such as the heat from boiling, frying, steaming, etc. Food processing often has effects on the nutrients in foods as well as the toxic components such as lectins (Udeogu and Awuchi, 2016; Awuchi *et al.*, 2019; Awuchi and Nwakwere, 2018), as well as functional properties such as refractive index (Awuchi *et al*., 2018), water absorption, etc. The effect of cutting vegetables may be seen from the exposure to light and air. Water-soluble vitamins such as the vitamins B and C dissolve into water when vegetables are boiled, and are lost once the water is discarded.

Table 1: Effects of cooking on vitamins

Vitamin	Soluble in Water	Stable to Heat Exposure	Stable to Light Exposure	Stable to Air Exposure
A	No	relatively stable	Partially	partially
C	very unstable	no	No	yes
D	No	no	No	No
E	No	no	Yes	yes
K	No	no	Yes	No
Thiamine (B_1)	highly	> 100 °C	?	No
Riboflavin (B_2)	slightly	no	in solution	No
Niacin (B_3)	Yes	no	No	No
Pantothenic Acid (B_5)	quite stable	yes	No	No
Vitamin B_6	Yes	?	Yes	?
Biotin (B_7)	somewhat	no	?	?
Folic Acid (B_9)	Yes	at high temp	when dry	?
Cobalamin (B_{12})	Yes	no	Yes	?

2.6 Recommended levels of vitamins intake

In setting the guidelines for human nutrients, government organizations do not certainly agree on amounts required to avoid deficiency or the maximum amounts to prevent the risks of toxicity. For instance, for vitamin C, the recommended intakes ranged from 40 mg per day in India to 155 mg per day for the European Union (EFSA, 2017). Table 2 shows U.S. Recommended Dietary Allowances (RDAs) and Estimated Average Requirements (EARs) for vitamins, the PRIs for the European Union (same conception as RDAs), followed by the amount three government organizations deem safe upper intake. RDAs are set above EARs to cover individuals with higher than average requirements. Adequate Intakes (AIs) are set when no sufficient information to establish RDAs and EARs exist. Governments are often slow to revise information of like this. For the U.S. values, with exception of vitamin D and calcium, all of the data date to 1997 to 2004 (Institute of Medicine's Food and Nutrition Board, 2020).

Table 2: Recommended levels for vitamins intake

Nutrient (Vitamin)	Unit	Highest U.S. RDA or AI	U.S. EAR	Highest EU PRI or AI	Upper limit (UL) U.S.	EU	Japan
Vitamin A	µg	900	625	1300	3000	3000	2700
Vitamin C	mg	90	75	155	2000	ND	ND
Vitamin D	µg	15	10	15	100	100	100
Vitamin K	µg	120	NE	70	ND	ND	ND
α-tocopherol (Vitamin E)	mg	15	12	13	1000	300	650-900
Thiamin (Vitamin B1)	mg	1.2	1	0.1 mg/MJ	ND	ND	ND
Riboflavin (Vitamin B2)	mg	1.3	1.1	2	ND	ND	ND
Niacin (Vitamin B3)	mg	16	12	1.6 mg/MJ	35	10	60-85
Pantothenic acid (Vitamin B5)	mg	5	NE	7	ND	ND	ND
Vitamin B6	mg	1.3	1.1	1.8	100	25	40-60
Biotin (Vitamin B7)	µg	30	NE	45	ND	ND	ND
Folate (Vitamin B9)	µg	400	320	600	1000	1000	900-1000
Cyanocobalamin (Vitamin B12)	µg	2.4	2	5	ND	ND	ND

AI US and EFSA Adequate Intake; the AIs established when there is no sufficient information to set EARs and RDAs.

EAR US Estimated Average Requirements.

ND ULs have not been determined.

NE EARs have not been established.

PRI Population Reference Intake is the European Union equivalent of the RDA; higher for the adults than for the children, and may be higher for women either pregnant or lactating. For Niacin and Thiamin the PRIs are expressed as amounts per MJ of calories eaten. MJ = megajoule = 239 food calories.

RDA US Recommended Dietary Allowances; higher for the adults than for children, and may be higher for women either pregnant or lactating.

Upper Limit or **UL** Tolerable upper intake levels.

2.7 Vitamins supplementation

In individuals who are otherwise healthy, there is a little evidence that vitamin supplements have any benefits with regard to cancer or heart disease (Moyer, 2014; Jenkins *et al.*, 2018). Vitamin A and E supplements do not only provide no health benefits for general healthy people, but they may increase mortality rates, though the two large studies which support this conclusion involved smokers for whom it was known already that beta-carotene supplements may be harmful

(Moyer, 2014; Bjelakovic *et al.,* 2007). A 2018 meta-analysis detected no evidence howsoever that intake of calcium or vitamin D for community-dwelling elderly individuals reduced bone fractures (Zhao *et al.*, 2017).

In Europe, there are regulations that define the limits of vitamins and minerals dosages for safe use as dietary supplements. Most of the vitamins sold as dietary supplements should not exceed maximum daily dosage known as the tolerable upper intake level (Upper Limit or UL). Vitamin products beyond these regulatory limits are not regarded as supplements and have to be registered as prescription medication or non-prescription (i.e., over-the-counter drugs) because of their potential side effects. The EU, the US and Japan establish Uls (Jenkins *et al.*, 2018; Bjelakovic *et al.,* 2007).

Dietary supplements usually contain vitamins, but can also include other beneficial ingredients, such as minerals, herbs (medicinal plants) (Awuchi, 2019a), and botanicals. Many scientific evidence supports the health benefits of dietary supplements for people with some health conditions. In certain cases, vitamin supplements might have unwanted effects, particularly if taken prior to surgery, with other medicines or dietary supplements, or if the individual taking them has some health conditions. They might also contain the levels of vitamins several times higher, and in diverse forms, than one may consume through food.

2.8. Governmental regulation

Most nations place dietary supplements in special category under general umbrella of foods, not as drugs. Consequently, the producer, and not government, has the responsibility to ensure that its dietary supplements products are safe before marketing. Regulation of supplements differs widely by country. In the US, a dietary supplement is clearly defined under the 1994 Dietary Supplement Health and Education Act (FDA, 2009a). There is no FDA process of approval for dietary supplements, and no requirements that producers prove the efficacy or safety of supplements introduced before 1994 (Wendt, 2015; Price, 2015). The FDA must depend on its Adverse Event Reporting System (AERS) to monitor adverse events which occur with supplements (FDA, 2009b). In 2007, the US CFR (Code of Federal Regulations) Title 21, part III took effect, regulating GMPs (Good Manufacturing Practices) in the manufacturing, labeling, packaging, or holding operations for the dietary supplements. Although product registration is not prerequisite, these regulations mandate standards for production and quality control (including testing for identity, adulterations, and purity) for dietary supplements. In the EU, the Food Supplements Directive (FSD) requires that only the supplements that have been confirmed safe can be sold without prescription. For most of the vitamins, pharmacopoeial standards were established. In the US, the US Pharmacopeia (USP) sets the standards for the most often used vitamins and preparations thereof. Similarly, monographs of the European Pharmacopoeia (the Ph.Eur.) regulate aspects of the identity and purity for vitamins within the European market. As seafood is a vital source of nutrients including micronutrients, government policies aimed at protecting aquatic life and environment are also required to ensure seafood sustainability (Awuchi and Awuchi, 2019a; Awuchi and Awuchi, 2019b). Table 3 lists chemicals that had earlier been classified as vitamins, and the previous names of vitamins which later became part of the vitamin B complex.

2.9 Naming

Table 3: Nomenclature of reclassified vitamins

Previous name	Reason for name change	Chemical name
Vitamin B_4	DNA metabolite; synthesized in body	Adenine
Vitamin B_8	DNA metabolite; synthesized in body	Adenylic acid
Vitamin B_T	Synthesized in body	Carnitine
Vitamin F	Needed in large amounts (does not fit the definition of a vitamin).	Essential fatty acids
Vitamin G	Reclassified as Vitamin B_2	Riboflavin
Vitamin H	Reclassified as Vitamin B_7	Biotin
Vitamin J	Catechol nonessential; flavin reclassified as Vitamin B_2	Catechol, Flavin
Vitamin L_1	Nonessential	Anthranilic acid
Vitamin L_2	RNA metabolite; synthesized in body	Adenylthiomethylpentose
Vitamin M or B_c	Reclassified as Vitamin B_9	Folate
Vitamin P	from the mid-1930s to early 1950s	Flavonoids
Vitamin PP	Reclassified as Vitamin B_3	Niacin
Vitamin S	Nonessential	Salicylic acid
Vitamin U	Protein metabolite; synthesized in body	S-Methylmethionine

The reason the sets of vitamins directly skips from E to K is because the vitamins corresponding to the letters F to J were either discarded as false leads, reclassified over time, or renamed due to their relationship to B vitamin, which became a complex of vitamins, known as B complex vitamin (but currently split with numerical subscripts). The German-speaking scientists that isolated and defined vitamin K (along with naming it as such) did so for the reason that the vitamin is directly involved in blood coagulation following wounding (from *Koagulation*, a German word). At the time, most (not all) of letters from F to J were already assigned, so the use of letter K was regarded quite reasonable.

The omitted B vitamins were determined not to be vitamins or reclassified. For instance, B_9 is folic acid and the five of the folates are within the range B_{11} to B_{16}. Others, such as the PABA (previously B_{10}), are toxic, biologically inactive, or with unclassifiable effects in human, or not generally recognized as vitamins by the science community, such as highest-numbered, which most naturopath practitioners call the B_{21} and the B_{22}. Also, there are nine lettered B complex vitamins (for example, B_m). There are other D vitamins currently recognized as other substances, which most sources of same type number up to D_7. A controversial cancer treatment laetrile at one point was lettered as vitamin B_{17}. There seems to be no general consensus on any vitamins with the letter Q, R, T, V, W, X, Y or Z, neither are there substances officially assigned as vitamins N or I, though the latter might have been another form of one of other vitamins or known and named nutrient of other type.

3.0 Mineral (nutrient)

In nutrition context, minerals are inorganic elements required as essential nutrients by organisms/humans to carry out functions necessary for life (Zoroddu *et al.*, 2019; Awuchi, 2019b; Berdanier *et al.*, 2013; National Library of Medicine, 2016). However, four major structural elements in human body by weight (carbon, nitrogen, oxygen, and hydrogen), are normally not included in the lists of major nutrient minerals (but nitrogen is considered mineral for the plants, as it is often included in fertilizers). The four elements together compose around 96% of the weight of human body, and major minerals (called macroelements or macrominerals) and minor minerals (called trace elements or microelements) make up the remainder.

Being elements, minerals cannot be biochemically synthesized by living organisms/humans. Plants get their minerals from soil (Corvallis, 2016). Most of the minerals in human diets come from eating animals and plants or from drinking water (Corvallis, 2016). Total minerals in food is referred to as ash (Awuchi *et al.*, 2019; Awuchi, 2019b; Awuchi and Nwankwere, 2018). As a group, minerals are among the four groups of essential nutrients, others include vitamins, essential amino acids, and essential fatty acids (US National Institutes of Health, Bethesda, 2016). They are called essential nutrients because they cannot be synthesized in the body and therefore must be taken through foods or, in rare cases, supplements. The five major minerals (inorganic elements) in human body are calcium, sodium, magnesium, phosphorus, and potassium (Berdanier *et al.*, 2013). All of the remaining inorganic elements in human body are known as trace elements. The trace elements with specific biochemical function in human body are zinc, manganese, molybdenum, iodine, selenium, sulfur, iron, chlorine, cobalt, and copper (Berdanier *et al.*, 2016).

Most chemical elements consumed by organisms/humans are in form of simple compounds. Plants absorb dissolved elements from soils, which are subsequently consumed by the omnivores and herbivores that consume them, and the inorganic elements move up the food chain. The larger organisms may also ingest soil (known as geophagia) or use the mineral resources, such as the salt licks, to obtain minerals unavailable through other dietary sources.

The bacteria and fungi play essential role in weathering of primary elements that leads to the nutrients release for their own nutrition and for nutrition of other species in ecological food chain. An element, cobalt, is only available for use by animals after been processed into complex molecules (such as vitamin B_{12}) by bacteria. Minerals (inorganic elements) are used by the animals and the microorganisms for process of mineralizing structures, known as "biomineralization", used to form bones, exoskeletons, mollusc shells, seashells, and eggshells.

3.1 Essential inorganic elements for humans

At least 20 chemical elements (minerals) are known to be required by human to support biochemical processes by serving functional and structural roles as well as being electrolytes (Zoroddu *et al.*, 2019). Oxygen, hydrogen, carbon and nitrogen (O, H, C, and N) are the most abundant elements in human body by weight and make up around 96% of the weight of the human body. Calcium makes up 920 g to 1200 g of the body weight of an adult, with 99% of it contained in the bones and teeth. This is around 1.5% of body weight (Berdanier *et al.*, 2013). Phosphorus occurs in amounts of around 2/3 of calcium, and makes up around 1% of an individual's body weight (National Library of Medicine, 2016). The other major minerals (sodium, chlorine, sulfur, magnesium, and potassium) make up only approximately 0.85% of the weight of human body. Together these 11 chemical elements (O, Ca, P, K, Na, H, C, N, Cl, Mg, S) make up 99.85% of the human body. The remaining ~18 ultratrace minerals consist of just 0.15% of the human body, or about 1 g in total for the average individual.

Different opinions exist regarding the essential nature of several ultratrace elements in humans (and other mammals too), even based on same data. For instance, there is no scientific agreement on whether chromium is considered an essential trace element in human. The US and Japan designate chromium as essential nutrient (Institute of Medicine (US) Panel on Micronutrients, 2001), but the EFSA (European Food Safety Authority), representing the EU, reviewed the scientific question in 2014 and does not approve (European Food Safety Authority, 2014).

Most of the suggested and known mineral nutrients are of low atomic weight relatively, and are reasonably common on soil (land), or for iodine and sodium, in the ocean:

H																		He
Li	Be													B	C	N	O	F	Ne
Na	Mg													Al	Si	P	S	Cl	Ar
K	Ca	Sc		Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
Rb	Sr	Y		Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
Cs	Ba	La	*	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
Fr	Ra	Ac	**	Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg	Cn	Nh	Fl	Mc	Lv	Ts	Og
			*	Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu	
			**	Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr	

Legend:

- The 4 basic organic elements
- The quantity elements
- The essential trace elements
- Deemed essential trace element by the U.S., not by the EU
- Suggested function from the deprivation effects or the active metabolic handling, but unclearly biochemical function in the humans
- Limited circumstantial evidence for the trace benefits or biological action in the mammals

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No evidence for biological actions in mammals, but essential in a few lower organisms. (In the case of lanthanum, definition of essential nutrient as being irreplaceable and indispensable is not entirely applicable due to extreme similarity of lanthanides. Early lanthanides up to Sm are known for stimulating the growth of many lanthanide-using organisms.) (Daumann, 2019)

Figure 1: Nutritional elements in the periodic table

Table 4: Roles of minerals in biological processes

Dietary element	RDA (US) [mg]	UL (US and EU) [mg]	High nutrient density dietary sources	Term for deficiency	Term for excess	Category
Calcium	1200	2500; 2500	Dairy products, canned fish with bones (salmon, sardines), green leafy vegetables, eggs, nuts, tofu, thyme, oregano, dill, cinnamon, seeds.	hypocalcaemia	hypercalcaemia	Needed for heart, muscle, and digestive system health, builds bone, supports synthesis and function of blood cells
Chlorine	2300	3600; NE	Table salt (NaCl) is the main dietary source.	hypochloremia	hyperchloremia	Required for production of hydrochloric acid in stomach and in cellular pump functions
Chromium	0.035	NE; NE	Broccoli, grape juice (mostly red), meat, whole grain products	Chromium deficiency	Chromium toxicity	Involved in glucose and lipid metabolism, though its action mechanisms in the body and the amounts required for optimal health are inadequately defined
Cobalt	none	NE; NE	Essential in the synthesis of vitamin B_{12}, but as bacteria are required to synthesize the vitamin, it is commonly considered part of vitamin B_{12} that comes from consumption of animals as well as animal-sourced foods (eggs...)		Cobalt poisoning	
Copper	0.9	10; 5	Liver, seafood, nuts, oysters, seeds; some: whole grains, legumes	copper deficiency	copper toxicity	Required component of various redox enzymes, including the cytochrome c oxidase
Iodine	0.150	1.1; 0.6	Seaweed (kelp or kombu)*, eggs, iodized salt, grains	iodine deficiency	iodism Hyperthyroidism	Required for the synthesis of thyroid hormones, triiodothyronine and thyroxine and to prevent goiter: Iodine in biology

Iron	18	45; NE	Meat, seafood, nuts, beans, dark chocolate	iron deficiency	iron overload disorder	Required for many enzymes and proteins, notably the hemoglobin to prevent anemia
Magnesium	420	350; 250	Spinach, legumes, seeds, whole grains, nuts, peanut butter, avocado	hypomagnesemia, magnesium deficiency	hypermagnesemia	Required for processing ATP and for bones
Manganese	2.3	11; NE	Grains, seeds, nuts, legumes, leafy vegetables, tea, coffee	manganese deficiency	manganism	A cofactor in enzyme functions
Molybdenum	0.045	2; 0.6	Legumes, whole grains, nuts	molybdenum deficiency	molybdenum toxicity	The oxidases xanthine oxidase, sulfite oxidase, and aldehyde oxidase
Phosphorus	700	4000; 4000	Red meat, dairy foods, bread, rice, oats, fish, poultry. In biological contexts, usually seen as phosphate	hypophosphatemia	hyperphosphatemia	A component of bones, cells, in energy processing, in DNA & ATP (as phosphate) and various other functions
Potassium	4700	NE; NE	Sweet potato, tomato, potato, beans, seafood, banana, prune, lentils, dairy products, carrot, orange	hypokalemia	hyperkalemia	A systemic electrolyte and is also essential in coregulating ATP with sodium
Selenium	0.055	0.4; 0.3	Brazil nuts, seafoods, meats, grains, dairy products, eggs, organ meats	selenium deficiency	selenosis	Essential to activity of the antioxidant enzymes such as glutathione peroxidase
Sodium	1500	2300; NE	Table salt (sodium chloride, NaCl, the main source), milk, sea vegetables, and spinach.	hyponatremia	hypernatremia	A systemic electrolyte and is also essential in coregulating ATP with potassium
Zinc	11	40; 25	Oysters*, red meat, nuts, whole grains, poultry, dairy products	zinc deficiency	zinc toxicity	Pervasive and required for many enzymes such as carboxypeptidase, carbonic anhydrase, and liver alcohol dehydrogenase

UL = Tolerable upper intake level; RDA = Recommended Dietary Allowance; Figures shown are for adults age 31 to 50, male or female neither lactating nor pregnant

* One serving of seaweed exceeds the United States UL of 1100 µg but not the 3000 µg UL set by Japan (Minister of Health, Labour and Welfare, Japan, 2015).

3.2 Dietary nutrition

Dietitians and nutritionists may recommend that minerals (macroelements, trace elements, ultratrace minerals) are best supplied by consuming specific foods rich with the element(s) of interest. The minerals may be naturally present in the diet (e.g., calcium in milk) or added to it (e.g., iodized salt fortified with iodine; orange juice fortified with calcium). Dietary supplements may be formulated to include several different minerals (as compounds), combination of vitamins and/or with other chemical compounds, or single element (as compound or the mixture of compounds), such as calcium (calcium citrate, calcium carbonate) or iron (iron bis-glycinate, ferrous sulfate) or magnesium (magnesium oxide).

The dietary focus on chemical elements grows from interests in supporting biochemical reactions of metabolism with required elemental components (Lippard and Berg, 1994). Appropriate intake levels of some chemical elements have been shown to be required to for optimal health maintenance. Diet can meet all the human body's requirements for chemical elements, although supplements may be used when some recommendations are inadequately met by food consumption. An example would be a food low in dairy products, and as a result not meeting the recommended calcium levels.

3.3. Elements considered possibly essential but not confirmed

Several ultratrace elements have been reported as essential, but such claims have often been unconfirmed. Definitive evidence for the effectiveness comes from characterization of biomolecule containing the element with testable and identifiable function. A problem with identifying efficacy is due to some elements are innocuous at a low concentration and are also pervasive (examples include nickel and silicon in dust and solid), so proof of efficacy is lacking as deficiencies are difficult to reproduce (Lippard and Berg, 1994). Ultratrace elements of various minerals such as boron and silicon are known to play a role but the precise biochemical nature is not known, and others such as arsenic are thought to play a role in health, but the evidence is very weak.

Table 5: Elements considered likely essential but unconfirmed

Element	Description	Excess
Arsenic	Essential in rat, goat, chicken, and hamster models, however no biochemical mechanism known in human.	arsenic poisoning
Boron	Boron is essential plant nutrient, required mostly for maintaining integrity of cell walls (Mahler, 2009). Boron has been indicated to be essential to complete life cycle in representatives of all the phylogenetic kingdoms, including the model species *Xenopus* laevis (African clawed frog) and *Danio rerio* (zebrafish). In animals, supplemental boron was shown to activate vitamin D and reduce calcium excretion.	Nontoxic
Bromine	Likely important to tissue development and basement membrane architecture, as a required catalyst to make collagen IV (Scott *et al.*, 2014).	bromism
Fluorine	Fluorine (in fluoride form) is not considered as an essential element because human does not require it to sustain life or for growth. Research shows that the primary dental benefits from fluoride occur at the surface from the topical exposure. Of the minerals presented in this	Fluoride poisoning

	table, fluoride is only one which the US Institute of Medicine established an Adequate Intake.	
Lithium	It is unknown whether lithium has physiological role in any species, however nutritional studies involving mammals have shown its importance to health, resulting in a suggestion that it can be classed as essential trace element.	Lithium toxicity
Nickel	Nickel is an essential constituent of many enzymes, including hydrogenase and urease (Berdanier *et al.*, 2016). Although not required by humans, many are thought to be needed by gut bacteria, such as urease needed by some varieties of Bifidobacterium. In human, nickel may be cofactor or structural component of some metalloenzymes involved in hydrolysis, gene expression, and redox reactions. Nickel deficiency depressed growth in pigs, sheep, and goats, as well as diminished circulating concentration of thyroid hormone in rats.	Nickel toxicity
Strontium	Strontium has been indicated to be involved in calcium utilization in the body. It promotes calcium uptake into the bone at moderate dietary strontium level, but a rickets-producing (rachitogenic) action at higher dietary level.	Rachitogenic (causing Rickets)
Other	Vanadium and silicon have established, though specialized, biochemical roles as functional or structural cofactors in other organisms, and are likely, even possibly, used by mammals (including human). In contrast, tungsten, early lanthanides, and cadmium all have specialized biochemical usages in some lower organisms, but the elements seem not to be used by humans. Other elements considered to be likely essential include rubidium, aluminium, germanium, and tin (Insel *et al.*, 2004).	Multiple

3.4 Ecology of minerals

Minerals can be bioengineered by bacteria that act on metals to catalyze dissolution and precipitation of minerals (Warren and Kauffman, 2003). Mineral nutrients are recycled by bacteria well distributed throughout the soils, oceans, groundwater, freshwater, and glacier meltwater systems worldwide (Warren and Kauffman, 2003). Bacteria absorb dissolved organic matter containing the minerals as they scavenge phytoplankton blooms. The mineral nutrients cycle via this marine food chain, from the bacteria and phytoplankton to the flagellates and zooplankton, which are afterwards eaten by other marine life (Warren and Kauffman, 2003; Awuchi and Awuchi, 2019b; Awuchi and Awuchi, 2019a). In terrestrial ecosystems, fungi play similar roles as bacteria, mobilizing the minerals from the matter inaccessible by other organisms, and then transporting the nutrients acquired to local ecosystems (Gadd, 2017).

4.0 Micronutrient deficiencies

Micronutrient deficiency (may also be referred to as dietary deficiency) is insufficiency of at least one of the micronutrients required for optimal human (and animal or plant) health. In humans and other animals micronutrient deficiencies include both deficiencies vitamins and minerals (Young, 2012), while in plants they refer to the deficiencies of the essential trace minerals. Micronutrient deficiencies affect over 2 billion individuals of all ages in both industrialized and developing countries. They are the cause of many diseases, exacerbate others and are known for having an important impact on global health. Important micronutrients include vitamins A, B_1, B_2, B_3, B_6, B_{12}, and C, and the minerals iodine, selenium, iron, zinc, calcium, fluorine (Theodore, 2010). Micronutrient deficiencies are linked with 10% of all deaths in children (Westport, 2012), and are therefore of distinctive concern to individuals involved with child welfare and care. Deficiencies of the essential vitamins and minerals such as Vitamin A, zinc, calcium, iron, etc., may be caused by prolonged shortages of nutritious diet or by infections such as the intestinal worms. They can also be caused or worsened when illnesses (such as malaria or diarrhoea) cause rapid nutrients loss through feces or vomit. Prolonged storage of foods and beverages usually affect the components of foods (Igwe *et al*., 2018a; Igwe *et al*., 2018b), including micronutrients.

4.1 Vitamin deficiencies

Vitamin deficiency (also called Avitaminosis or hypovitaminosis) is the condition of a prolonged lack of a vitamin. It can be primary deficiency or secondary deficiency. When caused by insufficient intake of vitamin it is classified as primary deficiency, while when caused by an underlying disorder such as diarrhea, malabsorption, etc., it is known as secondary deficiency. An underlying health disorder may be metabolic (as in genetic defect for converting the amino acid tryptophan to niacin) or from the lifestyle choices that increase vitamin requirements, such as smoking or excessive drinking of alcohol (Lee, 2000). Government guidelines on vitamin deficiencies advise some intakes for healthy individuals, with specific values for babies, women, men, the elderly, and during breastfeeding or pregnancy (National Institute of Health & Nutrition, Japan, 2010). Many nations have instructed and authorized vitamin food fortification programs to stop commonly occurring vitamin deficiencies (Food Fortification Initiative, 2017). On the other hand, hypervitaminosis refers to symptoms caused by the excessive intakes of vitamin beyond requirements, especially for the fat-soluble vitamins that accumulate in body tissues (EFSA, 2006).

The history of the discovery of the deficiencies of vitamins progressed over centuries from the observations that some conditions such as scurvy could be treated or prevented with some foods having high contents of a required vitamin, to the identification and description of precise molecules essential for life as well as health. During the 20^{th} century, many scientists were awarded the Nobel Prize in Chemistry or the Nobel Prize in Physiology or Medicine for their roles in discovery of vitamins (The Nobel Foundation, 2019).

4.1.1 Defining deficiency of vitamins

A number of counties have published the guidelines defining deficiencies of vitamins and advising specific intakes for healthy populations, with different recommendations for men, women, the elderly, infants, and during breast feeding and pregnancy including Canada, Japan, the EU, and the US. These documents are updated as more research is published. In the US, RDAs

(Recommended Dietary Allowances) were first set in the 1941 by Food and Nutrition Board (FNB) of the National Academy of Sciences (NAS). There were periodic updates, concluding in the Dietary Reference Intakes. As updated in 2016, the US FDA published tables that clearly defined the Estimated Average Requirements (EARs) and Recommended Dietary Allowances (US Food and Drug Administration, 2016). RDAs are higher to cover individuals with higher than the average requirements. Together, these are part of the Dietary Reference Intakes. For few vitamins, there is insufficient information to set the EARs and RDAs. For these purpose, an Adequate Intake is publicized, based on assumption that what healthy individuals eat is sufficient. Nations do not often agree on the exact amounts of vitamins required to safeguard against deficiencies. For instance, for vitamin C (ascorbic acid), the RDAs for the women for Japan, the EU (called Population Reference Intakes) and the United States are 100, 95 and 75 mg/day, respectively (European Food Safety Authority, 2017). India sets its own recommendation at 40 mg/day.

4.1.2 Individual vitamin deficiencies

4.1.2.1 Water soluble vitamins

- The deficiency of thiamine (Vitamin B_1) is especially common in countries which do not require the fortification of maize and wheat flour and rice to replace naturally occurring vitamin B_1 content lost to bleaching, milling, polishing, and other processing techniques. Severe deficiency of thiamine causes beriberi, which came to be prevalent in Asia as more individuals adopted a diet predominantly of white rice. Korsakoff syndrome and Wernicke encephalopathy are forms of beriberi. Excessive intake of alcohol can also cause vitamin deficiency, especially when chronic. Symptoms of deficiency include emotional disturbances, weakness and pain in the limbs, periods of irregular heartbeat, impaired sensory perception, and weight loss. Long-term deficiencies of vitamins can be life-threatening (American Academy of Family Physicians, 2019). Deficiency is assessed by urinary output and red blood cell status (Fact Sheet for Health Professionals, 2018).
- The deficiency of riboflavin (Vitamin B_2) is especially common in countries which do not require the fortification of maize and wheat flour and rice to replace naturally occurring vitamin B_2 content lost to bleaching, milling, cooking, polishing, and other processing techniques. Deficiency causes angular cheilitis (inflammation at the corners of the mouth), painful red tongue with sore throat, and chapped and cracked lips. Eyes can be itchy, bloodshot, sensitive to light, and watery. Riboflavin deficiency also results in anemia with red blood cells normal in size and hemoglobin contents, but reduced in number. This type of anemia is distinct from the anemia caused by deficiency of vitamin B_{12} or folic acid, which cause anemia (Fact Sheet for Health Professionals, 2018).
- The deficiency of niacin (vitamin B_3) causes pellagra, a reversible nutritional and wasting disease characterized by four typical symptoms often known as the four Ds: dementia, diarrhea, dermatitis, and death. The dermatitis occurs on skin regions exposed to sunlight, such as the backs of neck and hands. The deficiency of niacin is a consequence of diets low in both niacin and tryptophan (an amino acid), a precursor for vitamin B_3. Chronic alcoholism is contributing risk factor. A low plasma tryptophan is non-specific indicator, which means it can have other causes. Signs and symptoms of deficiency of niacin start to reverse within days of

oral supplementation of niacin in large amounts (Fact Sheet for Health Professionals – Niacin, 2019).

- Deficiency of pantothenic acid (vitamin B_5) is extremely uncommon. Symptoms include fatigue, irritability, and apathy (Fact Sheet for Health Professionals - Pantothenic acid, 2018).
- The deficiency of vitamin B_6 is very rare, although it can be observed in some conditions, such as the end-stage kidney diseases or the malabsorption syndromes, such as Crohn disease, celiac disease, or ulcerative colitis. The signs and symptoms deficiency of vitamin B_6 include microcytic anemia, dermatitis, electroencephalographic abnormalities, depression and confusion (Fact Sheet for Health Professionals - Vitamin B_6, 2018).
- The deficiency of biotin (vitamin B_7) is rare, although vitamin B_7 status can be compromised in chronic alcoholics and during pregnancy and breastfeeding. The decreased urinary excretion of vitamin B_7 and the increased urinary excretion of 3-hydroxyisovaleric acid are good indicators of deficiency of biotin than the blood concentration. Deficiency affects skin health and hair growth (Fact Sheet for Health Professionals - Biotin, 2017).
- The deficiency of folate (vitamin B_9) is common, and linked with many health problems, but primarily with the neural tube defects (NTDs) in the infants when the plasma concentrations in the mother were low during first third of pregnancies. The government-mandated food fortification with folic acid has decreased the incidence of NTDs by 25 – 50% in more than 60 nations using such fortification of food. Deficiency may also result from uncommon genetic factors, such as the mutations in MTHFR gene that result in compromised folate metabolism (Fact Sheet for Health Professionals - Folate, 2015). Cerebral folate deficiency is another rare condition wherein folate concentrations are low in brain despite being normal in blood (Gordon, 2009).
- The deficiency of cobalamins (vitamin B_{12}) can lead to pernicious anemia, methylmalonic acidemia, subacute combined degeneration of spinal cord, and megaloblastic anemia, among other conditions. Folate supplementation can mask the deficiency of vitamin B_{12}.
- The deficiency of ascorbic acid (vitamin C) is rare. As a result, no countries fortify food as means of preventing the deficiency of vitamin C. The historic importance of ascorbic acid deficiency relates to the occurrence on long sea voyages, when the ship supplies of foods had no good source of vitamin C. Deficiency results in scurvy when the plasma concentrations fall less than 0.2 mg/dL, while the normal plasma concentrations range is 0.4 – 1.5 mg/dL. The deficiency leads to weight loss, weakness, and general pains and aches. Longer-term depletion affects the connective tissues, bleeding from the skin, and severe gum disease (Fact Sheet for Health Professionals - Vitamin C, 2019).

4.1.2.2 Fat-soluble vitamins

- The deficiency of vitamin A can cause night blindness (nyctalopia) and keratomalacia, the latter resulting in permanent blindness if untreated. It is the leading cause of the preventable childhood blindness, afflicting over 250,000 to 500,000 undernourished children in the developing countries every year, about half of whom pass away within one year of becoming blind, because the deficiency of vitamin A also weakens the immune system in human and other organisms. The normal range is 30 – 65 μg/dL, but plasma concentration within this range is not good indicator of pending deficiency as the normal range is sustained till the liver storage is depleted. After it happens, plasma concentration of retinol falls to below 20 µg/dL, signifying state of vitamin A inadequacy (UNICEF, 2018).

- The deficiency of vitamin D is common. Many foods do not contain vitamin D, showing that deficiency will occur except people eat manufactured foods intentionally fortified with vitamin D or get sunlight exposure. It is typically diagnosed by measuring concentration of 25-hydroxyvitamin D (25(OH) D) in the plasma, which is the most accurate and correct measure of vitamin D stores in the body. Deficiency is defined as below 10 ng/mL, and insufficiency within the range of 10 to 30 ng/mL. The serum concentrations of 25(OH)D above 30 ng/mL are not constantly associated with increased benefit. The serum concentrations above 50 ng/mL can be cause for concern. The deficiency of vitamin D is a well-known cause of rickets, and is linked to numerous other health problems (Ross *et al.*, 2011).
- The deficiency of vitamin E is rare, occurring as consequence of abnormalities in the dietary fat metabolism (or absorption), such as defect in alpha-tocopherol transport proteins, rather than from diet low in vitamin E. The Institute of Medicine of the US defines deficiency as blood concentration below 12 µmol/L. Deficiency causes a poor conduction of electrical impulses along the nerves due to the changes in the nerve membrane structures and functions.
- The deficiency of vitamin K due to low dietary intakes is rare. Deficient state can be a result of the fat malabsorption diseases. The signs and symptoms can include bleeding gums, nosebleeds, heavy menstrual bleeding in women, and sensitivity to bruising. Newborn infants are special case. The vitamin K in plasma is low at birth, even if a mother is supplemented during pregnancy, as the vitamin is not transported through the placenta. The vitamin K deficiency bleeding (VKDB) as a result of physiologically low plasma concentrations of vitamin K is serious risk for the premature and term baby and young infants. If left untreated, consequences can result in brain damage or even death. The VKDB prevalence is reported at 0.25 – 1.7%, with higher risk in Asian people. The recommended preventive treatment is intramuscular injection of 1 milligram of vitamin K at birth (known as the *Vitamin K shot.*) (CDC, 2017). There are protocols for oral administration of vitamin K, but intramuscular injection is preferred (Mihatsch *et al.*, 2016).

4.1.3 Prevention

4.1.3.1 Food fortification

Food fortification is a process by which micronutrients (essential trace elements and vitamins) are added to food often as a response to public health policy which aims at reducing the number of individuals with dietary deficiencies within a given population. Staple foods of any region can lack specific nutrients due to the composition of the soil of the region or from an inherent insufficiency of a normal food. Addition of micronutrients to condiments and staples can prevent the large-scale deficiency diseases.

As defined by the WHO (World Health Organization) and the United Nations FAO, fortification of food refers to the practice of intentionally increasing the content of any essential micronutrient (vitamins and minerals) in food regardless of whether the micronutrients were originally in the food already before processing or not, in order to improve nutritional quality of the food supply and also to provide public health benefit with reduced risks to health, while enrichment is defined as being synonymous with food fortification and refers to the intentional addition of micronutrients to food which are lost during the processing. The Food Fortification Initiative (FFI) lists all the countries in the world which conduct fortification programs, and within every country, what micronutrients are added and to which foods. Vitamin fortification programs exist in some countries for folate, thiamin, vitamin A, vitamin B_6, niacin, riboflavin, vitamin B_{12}, vitamin E, and vitamin D. Eighty one (81) countries required fortification of food with one or more vitamins as of December 21, 2018,. The most usually fortified vitamin (as used in 62 nations) is folate; wheat flour is the most commonly fortified food.

4.1.3.2 Genetic engineering (Genetic modification)

Starting in 2000, rice was genetically engineered experimentally to produce more than normal beta-carotene contents, giving it an orange/yellow color. The product is known as golden rice (*Oryza sativa*) (Federico and Schmidt, 2016). Biofortified sweet potato, cassava, and maize were other crops introduced to improve the beta-carotene content and content of some minerals (Talsma *et al.,* 2017*;* Mejia *et al.,* 2016).

When eaten, beta-carotene, a provitamin, is converted to vitamin A (retinol). The concept is that in regions of the world where the deficiency of vitamin A is common, growing and consuming this rice would reduce the rate of vitamin A deficiency, mostly its effect on the problems of childhood vision. As at 2018, the fortified golden crops were still in process of government approval, and were being assessed for the taste and education regarding their health benefits to improve acceptability and adoption by the consumers in impoverished countries (Talsma *et al.,* 2017).

4.1.4 Hypervitaminosis

Some vitamins cause chronic or acute toxicity, a condition known as hypervitaminosis, which occurs mostly for fat-soluble vitamins if consumed excessively, mostly by excess supplementation. Hypervitaminosis A (National Library of Medicine, 2019) and hypervitaminosis D (National Library of Medicine, 2019) are the most common examples. The toxicity of vitamin D does not result from consuming foods rich in vitamin D or sun exposure, but rather from the excessive intake of vitamin D supplements, likely resulting in hypercalcemia, kidney stones, nausea, and weakness (Katherine, 2018). The US, Japan, and the EU, among other countries, have established ULs (tolerable upper intake levels) for the vitamins which have known toxicity.

4.2. Mineral deficiencies

Mineral deficiency is lack of dietary minerals, the micronutrients required for proper health. Of human and other organisms. The cause may be poor diet, dysfunction in the use of the mineral after absorption, or impaired uptake of the minerals consumed. These deficiencies can result in several disorders including goitre and anemia. Examples of mineral deficiency include iron deficiency, magnesium deficiency, zinc deficiency, calcium deficiency, etc. Mineral deficiencies negatively affect billions of people worldwide, imposing heavy burden on economic productivity and well-being. Most prominently, deficiencies in iodine iron, and zinc, have the largest negative impact on the public health; though, other minerals, including calcium, fluorine, magnesium, and selenium, significantly contribute to the health burden. Some mycotoxins such as aflatoxins, patulin, etc. may interfere with the elements in foods (Chinaza *et al*., 2019).

4.2.1 Zinc

Zinc is a constituent of numerous enzymes, and plays structural roles in proteins and also regulates gene expression. The deficiency of zinc in humans was first reported in 1960s in Iran and Egypt, where children and adolescent males with undeveloped genitalia and stunted growth responded to treatment with zinc (Jean, 2019). Deficiency of the micronutrient was attributed to the diet in the region, which was low in meat and high in unleavened breads, legumes, and whole-grain diets which contain phytic acid, fibre, and other anti-nutritive factors that inhibit the absorption of zinc. The practice of clay eating, which affects the absorption of zinc, iron, as well as other minerals also contributes to zinc deficiency. Severe deficiency of zinc has also been described in the patients fed intravenous solutions insufficient in zinc and in inherited zinc-responsive syndrome called acrodermatitis enteropathica (Theodore, 2010; Jean, 2019; Larry, 2018; Young, 2012; Westspot, 2012). Symptoms of zinc deficiency may include diarrhea, increased susceptibility to infections, skin lesions, night blindness, poor appetite, hair loss, reduced taste and smell acuity, slow wound healing, impotence, and low sperm count (Theodore, 2010; Jean, 2019; Young, 2012; Westspot, 2012). Zinc is highest in the protein-rich foods, particularly red meat and shellfish. Zinc status could be low in protein-energy malnutrition. In developed countries, young children, the elderly, strict vegetarians, pregnant women, people with alcoholism, and individuals with malabsorption syndromes are even vulnerable to deficiency of zinc.

4.2.2 Calcium

Almost all calcium in the body is in bones and the teeth, the skeleton serving as reservoir for calcium required in blood and elsewhere. During the childhood and the adolescence stages, adequate intake of calcium is critical for the bone growth and calcification. A low intake of calcium during childhood, and especially during adolescent growth spurt, may predispose individual to osteoporosis (a disease characterized by a reduced bone mass) later in life (Theodore, 2010; Young, 2012). As bones lose density, they develop fragility and inability to withstand ordinary strains; resulting fractures, mostly of the hip, may result in incapacitation and even death (Jean, 2019). Osteoporosis is mainly common in postmenopausal women in industrialized societies. Some processes foods undergo reduce the nutrients in them, including calcium (Awuchi and Nwankwere, 2018). Not a disease of calcium deficiency per se, osteoporosis is heavily influenced by heredity; the risks of the disease can be reduced by ensuring sufficient calcium intake all through life and doing regular weight-bearing exercise (Theodore, 2010; Jean, 2019; Young, 2012; Westspot, 2012). Sufficient calcium intake in immediate postmenopausal years does seem to slow bone loss, though not to the same degree as do bone-conserving drugs.

4.2.3 Chloride

Chloride is also lost from the body under the conditions that parallel those of loss of sodium. Severe chloride depletion results in condition known as metabolic alkalosis (excessive alkalinity in body fluids) (Jean, 2019). Table salt (sodium chloride) is excellent source of chloride.

4.2.4 Potassium

Potassium is widely distributed in food and the deficiency in the diet is rarely. However, some diuretics used in treatment of hypertension usually deplete potassium. Potassium is also lost during sustained diarrhea or vomiting or with chronic use of laxatives. The symptoms of potassium deficiency include muscle cramps, confusion, weakness, and loss of appetite. Severe low blood potassium (hypokalemia) may result in cardiac arrhythmias (Jean, 2019). Potassium-rich foods, such as bananas and oranges, can help replace potassium losses, as can potassium chloride supplements, which ought to be taken under medical supervision (Theodore, 2010; Jean, 2019; Young, 2012; Westspot, 2012).

4.2.5 Iron

Iron deficiency is the most commonly encountered among all nutritional deficiencies, with much of the population of the world being deficient in the mineral to some extent. Premenopausal women and young children are the most vulnerable to iron deficiency. The main function of iron is in hemoglobin formation, the red pigment of the blood which carries oxygen from lungs to other tissues in the body. Since every milliliter of blood contains 0.5 milligram of iron (as a hemoglobin component), bleeding drains the body's iron reserves (Theodore, 2010; Jean, 2019; Young, 2012; Westspot, 2012). When iron stores get depleted a condition known as microcytic hypochromic anemia arises, characterized by small red blood cells which contain less hemoglobin than usual. Symptoms of severe iron deficiency anemia are pale skin, difficulty breathing on exertion, fatigue, weakness, apathy, and low resistance to cold temperatures (Jean, 2019). During childhood, iron deficiency can affect the behavior and learning abilities as well as development and growth. Severe anemia increases the risks of maternal death and pregnancy complications. Iron deficiency anemia is mostly common during early childhood and late infancy, when iron stores present from birth have been exhausted and milk, which is very poor in iron, is a main food; during the adolescent growth spurt; as well as in women during childbearing years, due to blood loss during menstruation and the additional iron requirements of pregnancy (Theodore, 2010; Jean, 2019; Young, 2012; Westspot, 2012). Intestinal blood loss and the subsequent iron deficiency anemia in adults can also stem from ulcers, tumours, hemorrhoids, (Jean, 2019) or chronic use of some drugs such as aspirin. In developing nations, blood loss due to hookworm and some other infections, coupled with insufficient dietary iron intake, worsens iron deficiency in both adults and children.

4.2.6 Iodine

Iodine deficiency disorders are the utmost common cause of preventable brain damage, affecting an estimated 50 million people all over the world. During pregnancy, severe deficiency of iodine may impair fetal development, and results in cretinism (an irreversible mental retardation with developmental abnormalities and short stature) as well as in miscarriage or stillbirth (Theodore, 2010; Jean, 2019; Young, 2012; Larry, 2018). Other more prevalent consequences of chronic deficiency of iodine are lower cognitive and neuromuscular deficits. Ocean is a reliable source of iodine, but further than coastal areas iodine in food varies and largely reflects the quantity in soil. In chronic deficiency of iodine the thyroid gland enlarges due to its attempts to trap more and more iodide (a form in which the iodine functions in the body) from blood for the synthesis of thyroid hormones; it eventually grows into a visible lump at the front of the neck, a condition known as a "goitre". Many foods, such as cassava, sweet potato, certain beans, millet, and members of cabbage family, contain substances called goitrogens which interfere with thyroid hormone synthesis. The substances, although destroyed by cooking, may be a significant factor in people with coexisting deficiency of iodine who depend on goitrogenic foods as staples. Ever since the strategy of worldwide iodization of salt was adopted in the year 1993, there has been remarkable progress in the improvement of iodine status worldwide (Jean, 2019; Larry, 2018). Nonetheless, millions of individuals living in iodine-deficient areas, mostly in Central Africa, Central and Southeast Asia, and even in Eastern and Central Europe, remain at risk.

4.2.7 Fluoride

Fluoride contributes to the bones and teeth mineralization and protects against tooth decay. The epidemiological studies in the US in the 1930s and 1940s showed an inverse association between the natural fluoride in water and the rates of dental caries (Jean, 2019). In areas where levels of fluoride in drinking water are low, prescribed fluoride supplements are recommended for the children older than 6 months; also dentists may apply fluoride gels or rinses periodically to the teeth of their patients (Theodore, 2010; Jean, 2019; Young, 2012; Westspot, 2012). Fluoridated toothpastes are important sources of fluoride for the children and also for the adults, who continue to benefit from intake of fluoride.

4.2.8 Sodium

Sodium is often provided in ample amounts by foods, even without additional table salt (sodium chloride). Additionally, the body's sodium-conservation mechanisms are greatly developed, and thus deficiency of sodium is rare, even for individuals on low-sodium diets (Theodore, 2010; Jean, 2019; Young, 2012; Westspot, 2012). Sodium depletion may occur during persistent heavy sweating, diarrhea, or vomiting, or in cases of kidney disease (Theodore, 2010; Jean, 2019; Young, 2012; Westspot, 2012). Symptoms of low blood sodium (hyponatremia), include muscle weakness, cramps, nausea, dizziness, and eventually shock and then coma. After protracted high-intensity exertion in the heat, the sodium balance can be restored through drinking beverages containing sodium and glucose (referred to as sports drinks) and by consuming salted food (Jean, 2019). Drinking 1 liter of water containing 2 ml (one-third teaspoon) of the table salt also should meet one's requirements.

5.0 Conclusion

Micronutrients are essential elements required by organisms in varying quantities throughout life to orchestrate a range of physiological functions to maintain health. Micronutrient requirements differ between organisms; for example, humans and other animals require numerous vitamins and dietary minerals, whereas plants require specific minerals. For human nutrition, micronutrient requirements are in amounts generally less than 100 milligrams per day, whereas macronutrients are required in gram quantities daily. Micronutrient requirements for animals also include vitamins, which are organic compounds required in microgram or milligram amounts. A vitamin is an organic molecule (or related set of molecules) that is an essential micronutrient that an organism needs in small quantities for the proper functioning of its metabolism. Essential nutrients cannot be synthesized in the organism, either at all or not in sufficient quantities, and therefore must be obtained through the diet. Vitamin C can be synthesized by some species but not by others; it is not a vitamin in the first instance but is in the second. Vitamins are classified as either water-soluble or fat-soluble. In humans there are 13 vitamins: 4 fat-soluble (A, D, E, and K) and 9 water-soluble (8 B vitamins and vitamin C). Water-soluble vitamins dissolve easily in water and, in general, are readily excreted from the body, to the degree that urinary output is a strong predictor of vitamin consumption. Because they are not as readily stored, more consistent intake is important. Fat-soluble vitamins are absorbed through the intestinal tract with the help of lipids (fats). Vitamins A and D can accumulate in the body, which can result in dangerous hypervitaminosis. Fat-soluble vitamin deficiency due to malabsorption is of particular significance in cystic fibrosis. Anti-vitamins are chemical compounds that inhibit the absorption or actions of vitamins. For example, avidin is a protein in raw egg whites that inhibits the absorption of biotin; it is deactivated by cooking. Pyrithiamine, a synthetic compound, has a molecular structure similar to thiamine, vitamin B_1, and inhibits the enzymes that use thiamine. In nutrition context, a mineral is a chemical element required as an essential nutrient by organisms to perform functions necessary for life. However, the four main structural elements in human body by weight (oxygen, carbon, hydrogen, and nitrogen), are generally not included in the lists of major nutrient minerals (but nitrogen is considered mineral for plants, as it is often included in fertilizers). The four elements compose around 96% of the human body weight, and major minerals (macro minerals) and minor minerals (also called trace elements) compose the remainder. The five major minerals in the human are calcium, potassium, sodium, magnesium, and phosphorus. All of the remaining elements in human body are known as trace elements. The trace elements which have specific biochemical function in the human body include sulfur, iron, copper, zinc, manganese, molybdenum, chlorine, cobalt, iodine, and selenium. Oxygen, carbon, hydrogen, and nitrogen are most abundant elements in the body by weight; they make up around 96% of the weight of human body. Calcium makes up 920 g to 1200 g of body weight of an adult, with 99% of it contained in the bones and teeth. This is around 1.5% of body weight. Phosphorus occurs in the amounts of around 2/3 of calcium, and makes up approximately 1% of an individual's body weight. The other major minerals (potassium, chlorine, sulfur, magnesium, and sodium) make up only around 0.85% of the body weight. Together these eleven chemical elements (P, K, Na, Cl, H, C, N, Mg, O, Ca, S) make up 99.85% of the human body. The remaining ~18 ultratrace minerals make up just 0.15% of the body, or about 1 g in total for the average individual. Micronutrient deficiency is not enough of at least one of the micronutrients needed for optimal health. In humans and animals they include both deficiencies of vitamins and minerals. Vitamin deficiency is the condition of prolonged lack of vitamin. When caused by insufficient intake of vitamin it is classified as *primary deficiency*, while when due to an underlying health disorder such as malabsorption it is known as *secondary deficiency*. Conversely hypervitaminosis is the symptoms caused by excess vitamin intakes, especially for the fat-soluble vitamins that accumulate in body tissues. Mineral deficiency is lack of dietary minerals, the micronutrients needed for proper health. The cause can be poor diet, impaired uptake of minerals consumed or dysfunction in the use of mineral after it is absorbed. Mineral deficiencies negatively affect billions of people worldwide, imposing heavy burden on well-being and economic productivity. Most importantly, deficiencies in zinc, iodine, and iron have the largest negative effect on the public health; however, other minerals, including selenium, fluorine, calcium, and magnesium, contribute significantly to the health burden. Food fortification, genetic engineering, and micronutrient supplementation are the major ways of tackling micronutrients deficiencies.

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