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Abstract

Studies in the last two decades show the relationship between malnutrition and the debility of some diseases. While some scholars believe it contributes to the virulence of infectious diseases, others opine that it plays a role in the deteriorating conditions of some metabolic or noncommunicable diseases. In recent times, the term malnutrition has been expanded to cover a broader spectrum, ranging from the double burden, which includes undernutrition and overnutrition, to the triple burden, in which the duo and micronutrient deficiency are considered. This review elaborates on the broader definition of malnutrition, the determinants of malnutrition, the triple burden of malnutrition coupled with the tandem effects of malnutrition on the immune system. Where possible, we used examples to clarify and conceptualize this review, bringing in some real-life context in which these burdens are applicable. We discussed the cellular implications of the micronutrient deficiencies and buttressed using body mass index as a rough guide in estimating overweight and underweight.

Keywords: malnutrition, overnutrition, undernutrition, micronutrient deficiency, colony collapse disorder, body mass index, failure to thrive, Kwashiorkor, Marasmus

1. Introduction

The major forms of malnutrition include undernutrition, overnutrition, and micronutrient deficiency (Figure 1). Undernutrition may be presented as wasting, stunting, and underweight; micronutrient deficiency is characterized by inadequate vitamins or minerals; and overweight, which includes obesity, is marked with an above 25 for the body mass index (BMI). These conditions all culminate in diet-related noncommunicable diseases, which, adversely impact the immune system, and give a leeway to infectious diseases. Malnutrition also implies the stark absence, excess, or diminished levels of nutrients such as energy-giving foods, proteins, and micronutrients, which have detrimental effects on the body. In some cases, two forms of malnutrition can be found: undernutrition and micronutrient deficiency or overnutrition and micronutrient deficiency. Malnutrition predisposes one to several diseases resulting in cellular dysfunction, which heralds organ malfunctioning [1–6].

Statistics as of 2020 shows that the burden of malnutrition is far from being solved, most especially among countries with low and middle income, where about 400
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Figure 1.
A figure showing the three burdens of malnutrition.

2 million children are micronutrient-deficient, and 200 million children are affected by stunting or wasting [5]. Hence, this review centralizes on the determinants or causes of malnutrition, the triple burden of malnutrition, and the effects of prolonged malnutrition on the immune system. This is done with the intent of identifying some of the challenges associated with malnutrition and also offering possible solutions.

2. Malnutrition

In 1956, Gmez and Galvan classified protein-energy malnutrition among children based on the percentage of expected weight for age. They categorized the children into three categories, which were first degree, second degree, and third degree. The children who, based on this calculation of the percentage of expected weight for age, have over 90% proximity to the expected (standard) value are considered normal or healthy. The first degree (mild malnutrition) falls between 76% and 90%. The second degree (moderate) falls between 61% and 75%, and the third degree (severe) is less than 60%. The major limitation with this classification is the inability to consider overweight as part of malnutrition. Hence, the popular choice of the classification method for malnutrition was proposed by John Conrad Waterlow in the 1970s. In this classification scheme, Waterlow combined height-for-age and weight-for-height data to show the effects of chronic malnutrition. The classification by Waterlow was preferred over that by Gmez et al. because it provides a very close estimate even when the child’s age is unknown [6–8].

The term malnutrition implies the intake of too little or too much of the needed nutrients by the body. This imbalance in nutrients can affect the functional and structural integrity of the cells. In malnutrition, nutrient deprivation leads to some types of diseases, which may manifest as weight loss, wasting, retarded growth, poor health conditions, and in some cases, obesity emanating from overnutrition. In general, “malnutrition” mainly refers to undernutrition; hence, this term may make it difficult to delineate between undernutrition and overnutrition. Some researchers opine that malnutrition should include all its forms; these researchers believe that obesity and undernutrition should be considered and grouped as double burdens [9]. Malnutrition among children is common among low-income households, especially in Africa and Asia. In the last decade, there has been a phenomenal increase in the population of children and women of child-bearing age in Africa and Asia affected by malnutrition [1, 2, 4].
Around 30% of people around the world suffer from malnutrition. It is estimated that stunting and wasting, characterized by undernutrition, are common in developing countries, while obesity and diet-related diseases are prevalent in developed nations. Due to their peculiar nutritional requirement, the prevalence of undernutrition among infants, children, and pregnant women differs in different studies [7]. This scenario could be due to various factors such as age, decreased dietary intake, and sensory decline, which also contribute to making the elderly at more risk of undernutrition. Between 2015 and 2020, the prevalence of malnutrition increased from over 750 million to over 800 million, perhaps due to the COVID-19 pandemic, which led to food shortages and spurred hunger globally. In 2020, about 150 million children were malnourished, and 45 million were wasted. In Asia, India has the highest rate of wasting among children. In Africa, the undernutrition burden is higher, especially among those under five. For instance, in Kenya, over 20% of the children are malnourished, while in Burundi, over 53% are affected [9–12].

2.1 Determinants of malnutrition

2.1.1 Enabling determinants

The enabling determinants are the basal cause of malnutrition (Figure 2). These determinants include political, social, financial, cultural, and environmental factors that foster good nutrition for women and children. The three categories of the enabling determinants, according to UNICEF, include good governance, sufficient

![Figure 2. A pyramid representing the determinants of maternal and child nutrition as adapted and modified from the conceptual framework of UNICEF. The pyramid's base is the most crucial determinant factor (base factor), and it greatly influences what happens to the other parts of the pyramid leading up to the outcome. Governance perhaps explains why we have more malnourished children in Africa and South Asia compared with western Europe.](image-url)
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resources, and positive societal norms [5]. According to experts, the prevalence of severe wasting and moderate hunger might have increased by 14% at the peak of the pandemic due to the policies regulating the control of COVID-19. This reduction in nutrition and health services could have contributed to an increased number of deaths among children under five years old in 2020 alone [13].

Enabling determinants such as climate change is considered one of the main factors disrupting global food supplies. The Intergovernmental Panel on Climate Change (IPCC) noted that the surge in temperatures in some regions is already inducing a prevalence of extreme weather conditions. Severe weather events, such as droughts, can significantly impact the nutritional status of the inhabitants of a country. For instance, during the 1998–2001 drought in Iran, about 80% of the livestock died. An increase in the frequency and intensity of extreme weather events such as drought in Sub-Saharan Africa would negatively affect the growth of crops and livestock in this region, leading to a drastic fall in the volume of food produced and culminating in food insecurity. This situation could mimic the colony collapse disorder, a natural phenomenon that occurs when bees die in large numbers [13, 14].

2.1.2 Underlying determinants

The underlying determinants are the second leading cause of malnutrition. These determinants are the food and nutritional packages offered to women and children in various households, communities, and environments. They are grouped into three categories, which are age-appropriate nutritious foods, age-appropriate feeding habits, and environment. The environment should be hygienic, disease-free, promote a healthy diet, and foster physical activity for all children and mothers [5]. In the diet of infants, the absence of breast milk may contribute to undernutrition, especially when infectious diseases such as malaria, measles, gastroenteritis, and pneumonia culminate in the exhaustion of nutrients in lactating mothers’ breastmilk, which triggers malnutrition. So can some chronic illnesses, especially HIV/AIDS, anorexia nervosa, and bariatric surgery, adversely affect the quality of health of the lactating mother and child [14].

2.1.3 Immediate determinants

The immediate determinants of maternal and child nutrition are diet and care, which are both synergistic (Figure 2). A good diet is motivated by adequate nutritious food and feeding to support a balanced diet for children and their mothers. The acts of care are seen in the practices and services performed to achieve this [5]. The link between varying socioeconomic status and poor health may be associated with good diet and care [12]. Food shortages can be caused by various factors, such as inadequate crop rotation and a lack of arable land. They can also occur in areas where the government and farming communities do not have the necessary resources to improve the yields. The World Bank and other donors have pressured developing countries to adopt free-market policies and urged them to reduce or eliminate their subsidies for agricultural inputs. Without government support, many farmers in developing countries cannot afford to buy fertilizer at market prices, and this causes low agricultural production and high food prices [14].

The outcome of the factors mentioned above results in the overall care of the growing child in the short and long term. For the children, it helps in their childhood and adolescence to ensure sound health of mind and body, which manifests as cognitive development and enhanced developmental strides. When the growth of a
child thrives well, the child becomes an adult with a sound mental state and physical attributes capable of working to contribute to a better society [5].

3. The triple burden of malnutrition

The triple burden of malnutrition is typical among children of low-income homes and some high-income homes, where a sedentary lifestyle may be the norm. It presents as overweight, underweight, and hidden hunger (micronutrient deficiency), as shown in Figure 1. These three burdens coexist in the same country and can even occur in the same household [15]. The determinants of malnutrition are the major causal factors of the triple burden of malnutrition, either directly or indirectly.

The effects of prolonged malnutrition include altered cellular metabolism, impaired cellular function, and loss of body tissues. Most of the time, malnutrition may present as muscular dysfunction, weakness, and altered immunity, which predisposes one to an increased risk of infection [16]. The burden of malnutrition can, in the long term, lead to serious health issues such as failure to thrive, stunted growth, obesity, eye problems, heart disease, and diabetes [17].

3.1 BMI

3.1.1 An index of choice

The National Institute for Health (NIH) transitioned to using BMI to define a person as underweight, normal weight, overweight, and obese instead of the traditional height vs. weight charts, perhaps due to its reproducibility. Two of the burdens in the triple burden can best be determined using BMI, while the third, the micronutrient deficiency, is in most cases ascertained via laboratory examination. The Body Mass Index (BMI), an index to detect if a person is underweight or overweight, was discovered by Adolphe Quetelet. The BMI is estimated by calculating a person’s weight in kilograms (kg), divided by the square of the height in meters (m). Hence, the unit is in Kg/m$^2$. It is grouped into severe underweight (< 16.5), underweight (16.5–18.5), normal weight (18.5–24.9), overweight (25–29.8), and obesity (≥ 30). The range of values given for BMI is consistent, although with some slight variations seen among regular athletes and people from Asia, especially South Asia [18, 19].

Based on the formula, the BMI of an adult whose height and weight are 1.7m and 60 kg, respectively, is 20.76 kg/m$^2$. Similarly, the BMI of a five-year-old child with the respective height and weight of 1 meter and 15 kg would be 15 kg/m$^2$. In this instance, one would rightly say that the adult is of normal weight while the child is underweight. However, it is important to note that BMI is only for screening and not for confirming overweight or underweight among children between ages 2 and 20.

3.2 Underweight: a low calorie-based malnutrition

Underweight occurs mostly due to a lack of access to nutritious food. It is mainly seen during scarcity of food, which pushes food prices high. Poverty is also a major contributing factor to the high number of malnourished children in developing nations [2–6]. It happens in three forms: wasting (low weight for height), stunting (low height for age), and underweight (low weight for age). Wasting and stunting are commonly found in children under five [2–5].
Underweight is weighing less than the normal amount for age, height, and build, and it is often diagnosed when the circumference of the mid-upper arm is less than 110 mm. Being underweight can result from stunting, where permanent, widespread damage to a child’s growth, development, and well-being is presented. In the first 1,000 days of post-uterine life, stunting presents with abysmal academic performance due to the limiting effects of malnutrition on brain development and the waned potency of the immune system culminating in absenteeism among these children [20]. Low height-for-age best defines stunting. It results from chronic or recurrent undernutrition induced by poverty, poor maternal health and nutrition, frequent illness, and/or inappropriate feeding and care in early life. Stunting prevents children from attaining their physical and cognitive growth [21].

Failure to thrive (FTT) is a classic but seldom consequence of being underweight in early childhood. Failure to thrive (FTT) is a commonly used term to describe the inability to gain adequate weight among pediatric-aged patients. The accepted definitions include a weight for age less than the fifth percentile on standardized growth charts, a loss in weight percentile of greater than two major percentile lines on the growth chart, or less than the 80 percentiles of median weight for height ratio weight/length ratio [21, 22]. Depending on the age of the child, the BMI is also applicable. The early treatment of this ailment is important because it can result in developmental delays and other long-term adverse effects on the developing child.

To efficiently treat, one needs to identify the etiology. The cause of failure to thrive may be multifactorial; however, it can collectively be grouped into decreased intake, increased output, and increased caloric demand. These categories can have organic or inorganic etiology. Organic causes may include dysphagia leading to the phobia of eating, chronic diarrhea leading to loss of calories and nutrients, or congenital heart failure precipitating increased caloric demands. While few organic causes exist, the inorganic causes appear to be more [21, 22]. The inorganic causes include exogenous reasons such as the improper composition of infant formula, imbalanced diet, severe anorexia, and parental neglect. Due to the inability to assimilate calories and nutrients, FTT has the potential to negatively impact the immune system.

Other cases commonly associated with being underweight among children, especially in Africa, are Kwashiorkor and Marasmus, which appear on the spectrum of protein-energy malnutrition. While Marasmus is characterized by severe weight loss, apathy, fatigue, dryness of skin, and hair loss, Kwashiorkor presents rashes, water retention, and bloated abdomen, which sometimes may lead to death if left untreated. Many cases presenting with undernutrition can be corrected using high-calorie foods and proteins.

3.3 Overweight: a lifestyle-induced malnutrition

Overnutrition (overweight or obesity) is a state in which an individual weight is an excess for the height; that is, there is an energy imbalance leading to excessive weight gain (energy input is greater than output). It is an abnormal or excessive fat accumulation that negatively affects health. It can be classified by BMI in adults and sometimes children older than 24 months. For adults, obesity is defined as BMI ≥ 30, while overweight is ≥ 25. Since BMI in adults does not correspond to the same degree of fatness in different individuals, it should be considered a rough guide [18, 19, 23]. Overnutrition is one of the leading causes of noncommunicable diseases such as arteriosclerosis, diabetes, hypertension, and cancer, among others [2–5].

The age of a subject needs to be considered when defining overweight and obesity. Overweight is defined as weight-for-height greater than two standard deviations
higher than the World Health Organization (WHO) Child Growth Standards, and 

obesity is defined as weight-for-height greater than three standard deviations above 

the WHO Child Growth Standards median for those younger than 5. For pediatrics 

between 5 and 19 years, overweight is BMI-for-age greater than one standard devia-

tion higher than the WHO Growth Reference median; and obesity is greater than two 

standard deviations higher than the WHO Growth Reference median [18, 19, 23].

The leading cause of obesity and overweight is an energy imbalance between the 

expended calories and consumed calories. Around the world, increased consump-

tion of energy-dense foods that are rich in fat and carbohydrates especially sweetened 

foods, starchy foods, and sugars is implicated. These high-calorie foods and a sedentary 

lifestyle are the key predisposing factors. The poor choice of diet and sedentary lifestyle 

are often an effect of societal norms, environment, and government policies [23].

The common health consequences associated with overweight and obesity 

are cardiovascular diseases, musculoskeletal diseases, and some types of cancer, 

including the prostate, liver, gallbladder, endometrial, breast, ovarian, kidney, and 

colon. A high BMI aggravates the risk for this aforementioned noncommunicable 

disease. Childhood obesity predisposes a child to a higher chance of obesity and 

disability in adulthood and, in some cases, premature death. Despite the chal-

lenges, obese children face, such as breathing difficulties, hypertension, cardio-

vascular disease, increased risk of fractures, insulin resistance, and psychological 

effects [23].

Supportive environments and communities motivate people to choose healthy 

living, such as eating healthier foods and indulging in regular physical activity to 

prevent overweight and obesity. These choices include reducing the number of fats 

and carbohydrates, increasing the protein-rich diets, replacing most high-calorie diets 

with fruits and vegetables such as whole grains, legumes, and nuts; and engaging in 

regular physical activity for an hour per day for children and 1.5 hours spread through 

the week for adults [23]. Experience has shown that fasting (and therapeutic hunger) 

could be a helpful modality. While some drugs for weight reduction may be designed 

using DNA, RNA, and synthetic proteins as platforms.

3.4 Hidden hunger: a micronutrient-based malnutrition

Hidden hunger, also known as the micronutrient deficiency, is the absence or 
lack of vitamins and minerals needed in trace amounts for the optimal functions of 

the cells [2–5]. It is a silent but salient determinant of the well-being of man. 

Micronutrient deficiencies can lead to visible and dangerous health conditions, 

although characterized by a less clinically notable decline in calorie level, mental 
alertness, and disease resistance; hence, it is said to be silent. This scenario, perhaps, 
could explain the reason for the name hidden hunger. Micronutrient deficiency is 
salient because its diminution or absence could lead to life-threatening conditions. 

Deficiencies in vitamin A, iron, and iodine are the most prevalent micronutrient 
deficiency around the world, particularly in children and pregnant women. Low- 
and middle-income counties remain the worst hit.

The need to fortify our foods with vitamins and minerals stems from various 
functions of micronutrients. These functions include enabling the body to produce 
hormones, enzymes, and other substances needed to optimize growth and develop-
ment. At the cellular level, micronutrients, mainly comprising vitamins and minerals, 
continue to serve as cofactors and play critical roles in the functionality and structure 
of the cells. At the tissue level, some of these nutrients contribute to blood formation
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and fortify the immune system [24]. Hence, experts in laboratory medicine have continued to appreciate its utility in health and disease.

There are about 30 micronutrients essential for the efficient functioning of the body system. Out of these micronutrients, there are those specially classified as immune boosters because of their indispensable role in fortifying the immune system. In addition to discussing the most common micronutrient deficiency in low-income countries, there is a need to elaborate on the five essential micronutrients needed for boosting immunity, considering the focus of the topic. These micronutrients are vitamin B6, C, E, magnesium, and zinc, and they maintain immune function.

3.4.1 Vitamin A deficiency (VAD)

VAD is mainly characterized by night blindness and xerophthalmia. It is the predominant cause of childhood blindness in the developing world, as it is estimated that around 250,000–500,000 children in low-income countries go blind each year due to this condition, while 13 million have varying degrees of visual impairment due to VAD. It commonly affects both women and children. Vitamin A deficiency in pregnant women mainly manifests as night blindness and, in extreme cases, stillbirth. The optimizing effects of vitamin A on the T cells of the immune system confers a certain level of immunity among children, reducing the likelihood of diseases such as measles and potentiating the effects of vaccines; hence, the need to ensure adequate levels of vitamin A among children [25–29].

Aside from diet-based deficiency and protein-energy malnutrition, other causes of VAD include alcoholism, iron deficiency, liver disorder, and inhibition of the retinol-binding protein (RBP) synthesis, which reduces retinol uptake [28–34]. Conversely, the overdose of vitamin A also has some negative effects, such as teratogenicity [30]. The most frequently used method to identify the levels of vitamin A is the High-Performance Liquid Chromatography (HPLC), and other methods involve the measurement of plasma retinol levels. The prevention and treatment of VAD are based on food fortification using vitamin A and intake of vitamin-A-based supplements [28–34]. The normal range of vitamin A is 20–60 mcg/dL or (0.69–2.09 micromol/L).

3.4.2 Iron deficiency

Iron serves as an electron receptor or electron donor, a feat which makes it an indispensable element in almost every biological process, prominent among them is the formation of hemoglobin. The popular iron-containing heme component of hemoglobin (Hb) needs iron to transport oxygen to the tissues from the lungs [35]. Iron is needed by myoglobin, a prototype of the hemoglobin to transport oxygen to the muscles. Iron is critical for the body to make hormones such as erythropoietin. Iron also contributes to an efficient metabolism by serving as a cofactor in some proteins and enzymes.

The overdose of iron, which could precipitate a free state of iron, leads to toxicity [35, 36]. Conversely, the prolonged deficiency of iron could elicit Iron-deficiency anemia, which presents with complications such as heart problems, pregnancy complications, retarded growth in children, fatigue, headaches, and paresthesia of extremities. Iron-deficiency anemia can also worsen a prevailing infectious disease, make other chronic conditions worse, or dampen the efficacy of the medications administered for these diseases [36]. Laboratory diagnosis for this deficiency includes full blood count and evaluation of serum ferritin levels, iron, total iron-binding capacity, and/or
transferrin. Normal range of Iron among males is 80–180 mcg/dL (14–32 μmol/L), females is 60–160 mcg/dL (11–29 μmol/L), and neonates is 100–250 mcg/dL.

3.4.3 Iodine deficiency

Iodine is an essential exogenous mineral needed by the thyroid gland to make thyroid hormones that control many functions in the body, including bone and brain development during pregnancy and infancy and growth and development through the stages of life [37]. Iodine is taken up in the form of iodide by the thyroid gland, salivary glands, gastric mucosa, and mammary glands in pregnant and breast-feeding women. Adequate levels of Iodine are needed to synthesize thyroid hormones thyroxine (T4) and triiodothyronine (T3). The iodide cycle consists of transport, oxidation, and coupling steps in thyroid follicular cells to produce thyroid hormones. Iodine plays a critical role in regulating the proliferation of thyrocytes and controlling the function of the thyroid in a phenomenon known as “autoregulation.” Excess iodine elicits a fall in thyroid blood flow, thyroglobulin proteolysis, and hormone secretion, and it also inhibits thyroid follicular cell growth in vivo and thyrocyte [38]. It enhances the development and function of the antigen-presenting cells (APCs), such as macrophages, dendritic cells, and B cells. It helps activate phagocytes and optimizes the actions of the natural killer cells, cytokines, and memory cells [39]. Molecular Iodine can have virucidal effects on some viruses, including vaccinia virus and coronavirus, especially SARS-CoV-2, as seen via experimental intranasal spray. It can also reduce the adverse effects associated with some vaccines, especially the mRNA vaccines [40]. The anti-inflammatory potential of Iodine is seen in its complex with povidone in povidone-iodine, where it neutralizes reactive oxygen species and shows antimicrobial effects [41].

The deficiency of iodine in childhood slows somatic growth and impedes cognitive and motor function [42]. This deficiency mostly leads to thyroid disease and, in severe cases, permanent brain damage and intellectual disability in babies; conversely, ingesting over 1.1 milligrams/day of iodine may lead to toxicity. Iodine toxicity may present as asymptomatic or overtly symptomatic thyroid dysfunction in patients with specific risk factors, such as those with underlying thyroid disease, the elderly, fetuses, and neonates [39]. Overdose of iodine may lead to hyperglycemia, hyperlipidemia, and hypertension [43]. Most foods provide approximately 190–210 μg/day for women and 240–300 μg/day for men; however, the recommended dietary allowance (RDA) for adult men and women is 150 μg/day.

3.4.4 Vitamin C deficiency

Vitamin C (ascorbic acid) is a six-carbon lactone electron donor produced from glucose by many animals. Some mammals’ livers and aves and reptiles’ kidneys are the major tissues that synthesize it. The substantial mutation of the gulonolactone (L-) oxidase pseudogene (GULOP) gene among primates led to the inability to produce the terminal enzyme L-gluconolactone oxidase in the biosynthetic pathway of ascorbic acid, obviating the synthesis of vitamin C [44–49]. As an antioxidant, it repairs worn-out tissues, enhances wound healing, replenishes the extracellular matrix (ECM), and optimizes the potency of the immune system. It also limits the spread of cancerous cells, quells inflammation, and reduces the incidence of cardiovascular disease. During the COVID-19 pandemic, some researchers noted that low levels of vitamin C were associated with the severity of the illness [50]. Some researchers also opined that
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Vitamin C helped in preventing the COVID-19 and also served as a remedy for this disease [44–49].

The deficiency of vitamin C is mainly associated with scurvy, which in extreme cases presents as dry hair and skin, anemia, gum, and dental problems. This deficiency can also lead to depression and cognitive impairment [51]. Due to the water-soluble nature of the vitamin, its toxicity is rare. The values outside the reference range of vitamin C, which is 0.6–2 mg/dL, can be detected by analyzing for ascorbic acid in blood samples.

3.4.5 Vitamin B deficiency

B vitamins are crucial to the optimal functioning of the cells, efficient metabolism and energy generation, genomic and non-genomic methylation, neurogenesis and neurodynamics, hematopoiesis, and regenerating and maintaining healthy tissues especially the skin, brain, and blood. The commonest function of all the B vitamins is seen in B12, which is vital for neurological function, DNA/RNA synthesis/repair, and red blood cell production by aiding in the production of hemoglobin. The B vitamins act as cofactors in enzymatic reactions. They are called stress vitamins because they help the body adjust to stress from mental, physical, pathological, or physiological exhaustion; hence, their need is increased under these conditions. Aside from vitamin B6 and B12, there is a need for regular intake of the B vitamins due to their water-soluble nature. The tissue stores of vitamin B12 in the liver last for several months, while that of vitamin B6 in the muscles lasts for few weeks; hence there could be a tendency to overdose on these two vitamins, despite their water-soluble nature [52, 53].

Vitamin B6, also known as the active form of pyridoxal phosphate (PLP), serves as a cofactor for about 160 reactions. Humans or other higher organisms do not produce this compound, but yeasts and bacteria can produce it, albeit in different ways. When supplied with food, the pyridoxal kinase (PDXK) in humans converts the pyridoxal, pyridoxine, and pyridoxamine in the food into active phosphates. The popular role of vitamin B6 is seen in the catabolism of glycogen, where it cooperates with glycogen phosphorylase, reactions catalyzed by amino acid synthases or (racemases), and amino acid transformations, where it is a coenzyme in transamination and decarboxylation reactions. The crucial pathways necessary for human health in which vitamin B6 is prominent are the metabolism of tryptophan, sphingosine phosphate, and the action of the transcription factor NF-κB. Research has shown that vitamin B6 can limit inflammation in the body by influencing the activity of the NLRP3 sensory protein associated with inflammasomes. PLP influences the renin-angiotensin system to regulate processes such as blood pressure, blood clotting, platelet aggregation, and endothelial integrity, which negatively impact human health if not properly controlled [54].

Higher vitamin B levels lead to nausea, indigestion, or diarrhea, which can be mild or severe depending on age and underlying pathology. The WHO recommends a daily intake of 1.3–1.7 mg for adults. Laboratory diagnosis is made by checking serum levels of respective B vitamins or the attendant effects seen in anemia. The reference range of vitamin B6 is 5–50 μg/L, while that of vitamin B12 is 160–950 pg/mL or 118–701 pmol/L.

3.4.6 Vitamin E deficiency

Vitamin E is a fat-soluble vitamin preserved in the adipose tissue, liver, and muscle. It mainly serves as an antioxidant, mopping up loose electrons called free radicals that can damage cells; thus, it can salvage the integrity of the blood and
blood vessels and strengthen the immune system. It functions in gene expression and cell signaling. The commonest form needed by the body is alpha-tocopherol; hence, vitamin E is also called alpha-tocopherol. The liver secretes this alpha-tocopherol under the regulatory influence of alpha-tocopherol transfer protein (α-TTP). Research has shown that missense mutations of some arginine residues at the surface of the α-TTP can induce severe vitamin E deficiency in humans. This study revealed that phosphatidylinositol phosphates (PIPs) in the target membrane promote the transfer of α-tocopherol by binding to the wild type of α-TTP, but this activity is lost with an arginine mutant α-TTP [55].

The deficiency of vitamin E implies that its antioxidant role is diminished. This rare condition is exclusive to people with a genetic or acquired inability to absorb the vitamin or difficulty in fat absorption or metabolism. Some rare conditions include Crohn’s disease, cystic fibrosis, short bowel syndrome or biliary obstruction, and a rare genetic disease such as abetalipoproteinemia and ataxia with vitamin E deficiency (AVED). This deficiency can lead to diseases such as aging, cancer, heart disease, arthritis, retinopathy, and sometimes impotence in males. It can cause increased production of prostaglandins such as thromboxane, which can lead to platelet clumping or platelet hyper-aggregation, which may culminate in atherosclerosis. It could lead to neurodegenerative diseases presenting as myopathies, spinocerebellar ataxia, dysarthria, diminished deep tendon reflexes, absence of both vibratory sensations and positive Babinski reflexes, and impaired thinking. Oxidative damage to the red blood cells precipitates severe hemolytic anemia, adversely affecting the immune system [55, 56].

Although vitamin E toxicity is rare, high doses could precipitate it. This toxicity may present with bleeding and muscle weakness, fatigue, nausea, and diarrhea. Diagnosis can be confirmed by analyzing the amount of alpha-tocopherol in red blood cells [57]. The reference range of vitamin E is 3–18.4 μg/mL in children and 5.5–17 μg/mL in adults.

3.4.7 Magnesium deficiency

Magnesium ions are critical in many processes associated with cellular metabolism. They contribute to stabilizing the structures of nucleic acids, proteins, and cell membranes by binding to the macromolecule’s surface and promoting specific structural or catalytic activities of proteins, ribozymes, or enzymes [58]. Its role in stabilizing the cells helps it fortify the immune system’s cells.

The magnesium toxicity presents with nausea, low blood pressure, muscle weakness, fatigue, and diarrhea. In high doses, severe complications include hypotension, cardiac arrest, and respiratory paralysis [59]. The normal value of magnesium ranges between 1.3 and 2.1 mEq/L (0.65–1.05 mmol/L). Laboratory diagnosis is via blood or urine.

3.4.8 Zinc deficiency

Zinc functions as an antioxidant via catalytic action of copper/zinc-superoxide dismutase. It is a redox-inert metal that is critical in protecting the protein sulfhydryl groups, membrane structure stability, and upregulation of the expression of metallothionein. The enzyme nicotinamide adenine dinucleotide phosphate oxidase (NADPH-oxidase) plays a key role in microbial killing via the innate immune system by producing reactive oxygen species (ROS), which, when excess, fuels inflammation.
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and oxidative stress, a process that necessitates the presence of zinc in inhibiting the action of NADPH-oxidase. This process also aids in proinflammatory response by aiming at the NADPH-dependent nuclear factor kappa B (NF-κB), a transcription factor that is the master regulator of proinflammatory responses. It potentiates the immune system’s actions and optimizes cell division, cell growth, breakdown of carbohydrates, and wound healing. It enhances the capacity to taste and smell via the taste buds and olfactory nerves. An adequate dose is needed during pregnancy, infancy, and childhood for proper growth and development [60–62].

Zinc deficiency is characterized by loss of appetite, growth retardation, and impaired immune function. In more severe cases, delayed sexual maturation, impotence, hair loss, diarrhea, hypogonadism in males, and eye and skin lesions. Zinc also shows a prooxidant effect when overdosed or deficient by increasing cellular oxidative stress due to its effect on NADPH-oxidase and NF-κB [63]. Low plasma and myocardial zinc levels could lead to reversible cardiomyopathy in people with nutritional deficiencies [64]. Zinc levels can be measured via body fluids and hair. However, zinc levels in neutrophils and the assay of activity of alkaline phosphatase in neutrophils may be the best diagnostic marker for the diagnosis of zinc deficiency [65]. The normal range of serum zinc levels in males is 59–125 μg/dL and 50–103 μg/dL for females (Table 1).

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<tr>
<th>Micronutrient</th>
<th>Function</th>
<th>Deficiency</th>
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<tbody>
<tr>
<td>Vitamin A</td>
<td>optimal vision</td>
<td>xerophthalmia and night blindness</td>
</tr>
<tr>
<td>Iron</td>
<td>Oxygen transport via Hemoglobin and Myoglobin</td>
<td>Iron-deficiency anemia</td>
</tr>
<tr>
<td>Iodine</td>
<td>Optimal production and function of thyroid hormones</td>
<td>Retarded somatic growth and brain damage</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Replenish ECM, and worn-out tissues</td>
<td>Scurvy, anemia</td>
</tr>
<tr>
<td>Vitamin B6</td>
<td>Catabolism of glycogen, transamination, and influences the action of NF-κB</td>
<td>Bleeding disorder and increased blood pressure</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>Blood formation, neurological function, DNA/RNA synthesis/repair</td>
<td>Pernicious anemia</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Gene expression and cell signaling</td>
<td>Neurodegeneration, hemolytic anemia</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Stabilizing the structures of nucleic acids, proteins, and cell membranes</td>
<td>Hypokalaemia</td>
</tr>
<tr>
<td>Zinc</td>
<td>Regulates NADPH-Oxidase and NF-κB, cell division, and growth</td>
<td>Retarded growth, immune suppression, and impotence</td>
</tr>
</tbody>
</table>

Table 1. A summary of the functions of the micronutrients with the highest prevalence of deficiency and those critical for optimal immunity.

4. Malnutrition and immunity: the tandem effects

The influence of malnutrition on our immune system cannot be overemphasized. For every malnutrition-based disease that plagues humans, there is an involvement of the interplay of the cells of immunity. This interplay of the cells of immunity
sometimes manifests as pyrexia in their quest to contain the inflammation associated with the improper functioning of the biological system. In malnutrition, the activation of the immune cells is enhanced, which may precipitate an increased systemic-inflammatory mediator level. However, malnutrition impairs the priming and presentation of antigens by the dendritic cells and monocytes and usurps the effector functions of memory T cells [66, 67]. Malnutrition also elicits decreased adipocyte mass, leading to diminished circulating leptin [68]. This diminution concurrently attenuates cell-mediated immunity; lowers the number of circulating T-lymphocytes, particularly CD4+ helper T-cells, CD8+ cytotoxic T-cells, and CD3+CD25+ T-cells that carry the interleukin (IL)-2 receptor; and induces hypo-stimulation of lymphocytes in response to mitogens and antigens [68, 69]. This plethora of effects on the immune system may culminate in autoimmunity.

In dire conditions of nutritional status (overweight, underweight, or hidden hunger), alterations in immune cell populations, hormones, and cytokine levels modulate the immune cell metabolism, which imparts the innate and adaptive roles of the immune system [68, 70]. Malnutrition wanes the resistance to infection, which subsequently aggravates malnutrition, especially as malnutrition presents with weight loss, compromised immunity, mucosal damage, susceptibility to diseases, and retarded growth in children [71]. Nutritional deficiency is associated with various infectious and metabolic diseases as a cause or consequence. Research shows that nutrients such as amino acids, short-chain fatty acids, and oligosaccharides elicit inhibitory and anti-inflammatory functions [72].

Globally, malnutrition has been identified as a leading cause of immunodeficiencies across all age groups, with neonates and geriatrics most affected. In the context of immunity, malnutrition can be grouped into protein-energy malnutrition and micronutrient deficiencies. Protein-energy malnutrition (PEM), a type of nutritional deprivation, is a predisposition to immunodeficiency, frequently leading to a severe infection, atrophied thymus, and wasting of peripheral lymphoid tissue and consequently hampers immune responses [73]. The malnutrition-based ailment is a major cause of morbidity across different age groups, and it is culpable for two-thirds of all deaths of children in their first 60 months of life in low-income nations [74, 75]. The major aim of a healthy diet is to maintain a functional immune system by avoiding immunodeficiency due to low-calorie intake, the overdose of calories, or micronutrient deficiencies. These high-nutrient diets synergize with an uncompromised immune system as they serve as support systems or cofactors needed to optimize the activities of this immune system.

5. Conclusion

Malnutrition may be broadly grouped into macronutrient-dependent, which is presented as underweight and overweight, and micronutrient-dependent. The dependency on macronutrients is determined by the availability of foods rich in fats, proteins, carbohydrates, and perhaps water, while that of micronutrients is related to the availability of vitamins and minerals. The impact of taking an inappropriate amount of macronutrients and micronutrients on the immune system best explains the relationship between malnutrition and immunity, an impact seen among people of all ages, although prominent in the first 60 months of life and toward the seventh decade of life. This impact is worsened in the face of food scarcity caused by wars and climate change; hence, the need for government intervention via policies.
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