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Combating Malnutrition through Sustainable Approaches

Edited by Farhan Saeed, Aftab Ahmed and Muhammad Afzaal

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Meet the editors

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Dr. Muhammad Afzaal is an Assistant Professor in the Department of Food Science at Government College University Faisalabad, Pakistan. In addition to his teaching responsibilities, he is also involved in various other assignments as a Business Manager-BIC and Lab Incharge (Food Safety and Biotechnology). Dr. Afzaal has accumulated around 10 years of teaching and research experience and has actively participated in numerous national and international research projects. He has over 100 publications to his credit, which include two books and ten book chapters. Dr. Afzaal has supervised twenty-five MS students and three Ph.D. students. He is a reviewer for several international journals and holds the position of Secretary in the Pakistan Society of Food Scientists & Technologists (PSFST), Faisalabad chapter, of which he is also a life member.

Contents

Preface

Malnutrition is becoming a major concern in developing countries due to a lack of facilities for post-harvest handling and improper supply chain management, because of which millions of tons of food are wasted each year. Shortage of food in many areas results in malnourished populations, especially children. According to recent statistics, more than 149 million children worldwide younger than 5 years were malnourished (wasted or obese) in 2020. Of these children, 3.1 million die every year due to the deficiency of vital nutrients, which leads to functional and structural abnormalities. This book provides a comprehensive overview of malnutrition and strategies for combatting this dangerous condition.

The book includes twelve chapters:

- Chapter 1: "Causes of Malnutrition"
- Chapter 2: "Inflammation-Based Markers of Nutrition in Cancer Patients"
- Chapter 3: "Energy Metabolism and Balance"
- Chapter 4: "Malnutrition and Sarcopenia"
- Chapter 5: "Perspective Chapter: Crop Biofortification – A Key Determinant towards Fighting Micronutrient Malnutrition in Northern Ghana"
- Chapter 6: "Fight Hidden Hunger through National Programs and Food Bases Approaches"
- Chapter 7: "Malnutrition's Prevalence and Associated Factors"
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- Chapter 10: "Perspective Chapter: Malnutrition and Air Pollution in Latin America – Impact of Two Stressors on Children's Health"
- Chapter 11: "Perspective Chapter: Sugar and Its Impact on Health"
- Chapter 12: Malnutrition: The Triple Burden and the Immune System

This book is a useful resource for scholars, researchers, and professionals, especially those affiliated with organizational institutes and nongovernmental organizations working to combat nutrient deficiency at all ages.

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Chapter 1

Causes of Malnutrition

Tariku Laelago Ersado

Abstract

Malnutrition is defined as deficiency or excess of nutrition consumption. It is can be undernutrition and overnutrition. Malnutrition contributed to more than third of child death. There is no single cause of malnutrition. The causes of malnutrition can be categorized as immediate, underlying, and basic. The immediate-level causes of malnutrition comprise inadequate dietary intake and disease conditions. The underlying-level causes include insufficient household food security, inadequate social and care environment and insufficient health service, and unhealthy environment. The basic-level causes of malnutrition consist climate variability and extremes, sociocultural, economic, and political context. Undernutrition is specifically caused by deficiency of energy, vitamin, and minerals. Overnutrition is specifically is caused by overconsumption of energy and micronutrients. The causes of overnutrition are not clearly put in many studies. Therefore, studies that focus on cause of overnutrition should be done by incorporating both developed and undeveloped countries.

Keywords: malnutrition, immediate, basic, underlying, causes, overnutrition, undernutrition

1. Introduction

Malnutrition refers to deficiencies or excesses in nutrient intake, imbalance of essential nutrients, or impaired nutrient utilization. Malnutrition can be divided into two types: undernutrition and overnutrition. Undernutrition manifests in four broad forms: stunting/chronic malnutrition, wasting/acute malnutrition, acute and/or chronic malnutrition/underweight, micronutrient deficiencies. Overnutrition consists of overweight and obesity [1, 2].

Wasting is defined as low weight for height. Wasting can be classified as severe acute malnutrition and moderate acute malnutrition. Severe acute malnutrition consists of kwashiorkor, marasmus and marasmic kwashiorkor. Wasting often shows current and severe weight loss, though it can also continue for a long time. It commonly happens when a person has not had food of adequate quality and quantity, and/or they have had frequent or prolonged illnesses. Wasting in children is related with a higher risk of mortality. Stunting is defined as low height for age. Stunting is the result of chronic undernutrition. It is related with poverty, poor maternal health and nutrition, illness, and feeding problems. It is the result of chronic or recurrent undernutrition, usually associated with poverty, poor maternal health and nutrition, frequent illness, and/or inappropriate feeding and care in early life. Stunting precludes children from attainment of their physical and mental potential. Underweight is defined as low weight for age. A child who is underweight may be stunted, wasted, or both. Micronutrient deficiencies are a lack of vitamins and minerals that are essential for body functions such as producing enzymes, hormones, and other substances needed for growth and development [2].

Malnutrition can be caused by various factors. Unavailability of enough food, having difficulty in eating or absorbing nutrient can cause malnutrition [3]. Health conditions such as vomiting, loss of appetite, mental health disorders, and some medicines can also cause malnutrition [4].

The causes of malnutrition can be grouped into immediate-level cause, underlying-level causes, and basic-level causes [5, 6]. Undernutrition can be particularly caused by consuming inadequate energy, vitamins, and minerals while overnutrition is caused by overconsuming energy and micronutrients [7]. The causes of malnutrition vary from place to place and from time to time. Availing updated information on causes of malnutrition is important to propose appropriate strategies that focus on prevention of malnutrition. The objective of this chapter is providing the best available and updated information on causes of malnutrition. The chapter described the causes of malnutrition by using different conceptual frameworks. The chapter also identified specific causes of malnutrition for common malnutrition types.

2. Causes of malnutrition

There is no single cause of malnutrition. Causes of malnutrition may range from individual, families, district, country, regions, and global level. The causes of malnutrition can be understood from UNICEF's conceptual framework and from conceptual framework developed for dry lands of Africa. Malnutrition causes can classified as immediate, underlying, and basic (**Figures 1** and **2**).

A new conceptual frame work developed for dry lands of Africa identified the basic/system, underlying, and immediate causes of acute malnutrition. The new

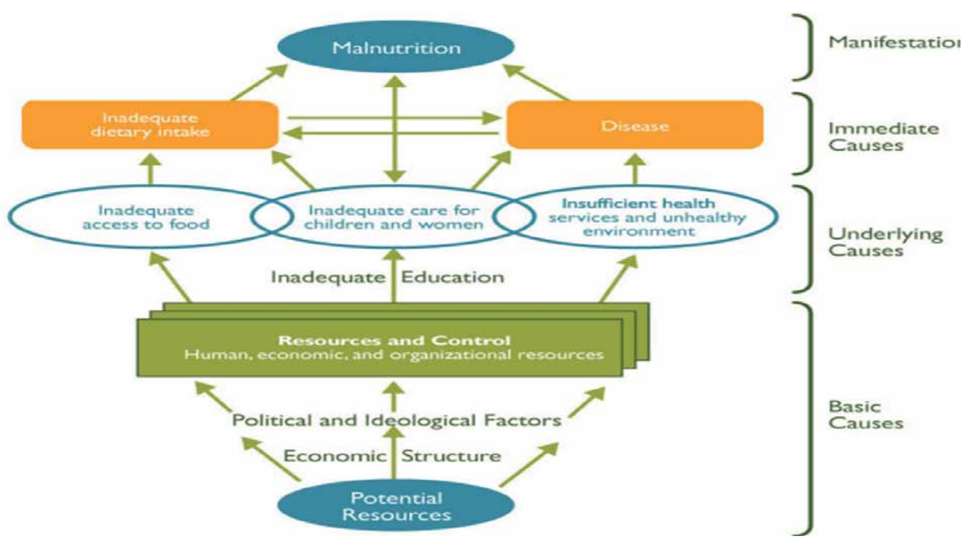

Figure 1.
UNICEF's conceptual framework for the cause of malnutrition. Source: Sablah [5].

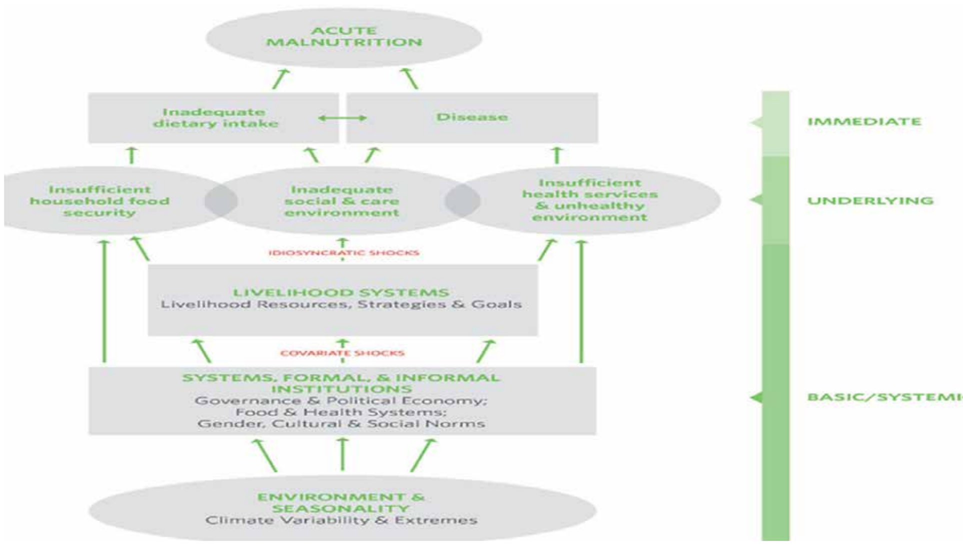

Figure 2.
Acute malnutrition in African dry land: a new conceptual framework for cause of malnutrition. Source: Young [6].

framework deals with acute malnutrition in African dry land [6]. The new conceptual framework focuses on the importance of climate and environment in dry lands in influencing livelihood systems. The conceptual framework also recognizes the deadly and often transformative impact of conflict and climate shocks on systems and institutions, livelihood resilience and adaptation, and the underlying causes of malnutrition. In reducing vulnerability and building resilience, the role of social and political systems, including governance, and within these systems, formal and informal institutions, is given renewed emphasis [6]. The manifestation of the new conceptual frame work is acute malnutrition. This is because severe acute malnutrition is a public health problem throughout the developing countries, mainly in Sub-Saharan Africa and South Asia.

2.1 Immediate-level causes of malnutrition

The immediate-level causes of malnutrition include inadequate dietary intake and diseases. On an immediate level, malnutrition results from an imbalance between the required amount of nutrients by the body and the actual amount of nutrients introduced or absorbed by the body. Inadequate dietary intake and diseases are caused by food insecurity, inadequate care for women and children, insufficient health services, and unsanitary environments [5]. Reduced dietary intake, reduced absorption of macro- and/ or micronutrients, increased losses or altered requirements, and increased energy expenditure (in specific disease processes) can be a cause for immediate malnutrition [8].

Dementia can cause a person to neglect their health and forget to eat. This in turn causes immediate malnutrition. Ulcerative colitis or Crohn's disease can also be a reason for malnutrition. People who have difficulty in eating due to painful teeth or lesions of mouth, dysphagia are also at risk of malnutrition. Loss of appetite that may be caused by cancers, tumors, mental illness, liver or kidney disease, chronic infections can also be included in immediate causes of malnutrition [9]. Diseases such as

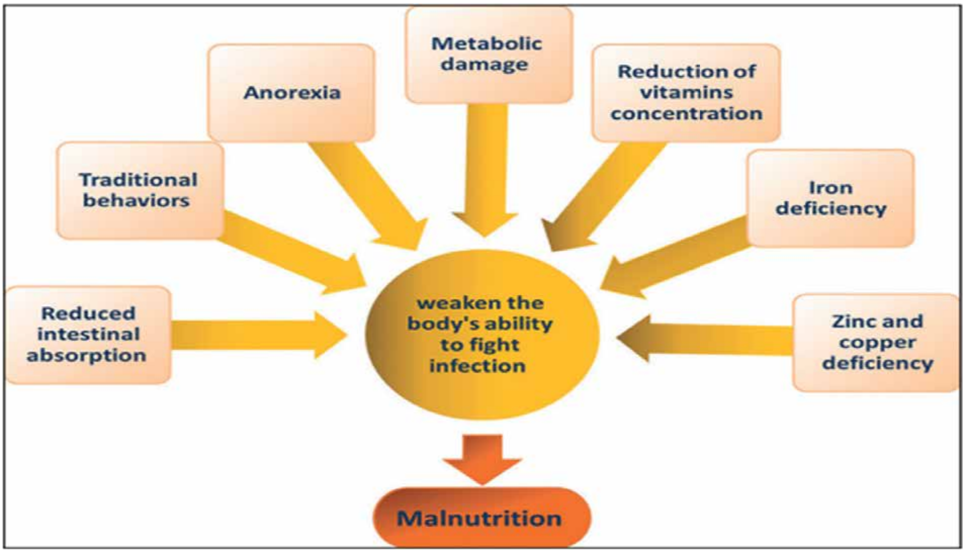

Figure 3.
The factors that weaken the body's ability to fight infection and cause malnutrition. Source: Farhadi and Ovchinnikov [11].

measles, diarrhea, AIDS, respiratory infection, malaria, renal failure, and intestinal worms can breakdown the nutritional status [10].

Anorexia, traditional behaviors, reduction of intestinal absorption, metabolic damage, disorder metabolism of lipids and carbohydrates, reduction of vitamins, iron, zinc, and copper can weaken the ability to fight infection and cause malnutrition. A large number of studies have illustrated a bidirectional interaction of malnutrition and infection (**Figure 3**) [11].

Health and nutrition are closely related in a "malnutrition-infection cycle" in which diseases contribute to malnutrition, and malnutrition makes an individual more vulnerable to disease. Malnutrition is the result of insufficient dietary intake, disease, or both. Disease contributes through loss of appetite, malabsorption of nutrients, and loss of nutrients through diarrhea or vomiting. If the body's metabolism is altered, greater the risk is of malnutrition (**Figure 3**).

In some circumstances, such as enterocutaneous fistulae or burns, patients may have excessive and/or specific nutrient losses; their nutritional requirements are usually very different from normal metabolism [8].

The pharmacological and pharmaceutical properties of drugs can affect the intake, digestion, absorption, storage, metabolism, and elimination of nutrients, causing imbalance in the amount of nutrients required in the body [12].

2.2 Underlying-level causes of malnutrition

Household (HH) food insecurity, poor social and care environment and poor access to health care, and unhealthy environment are included in underlying causes of malnutrition. The underlying issues are caused by conflict, inadequate education, poverty, gender inequality, inadequate infrastructure, and other basic issues [5].

HH food insecurity or the lack of food is a main factor that causes under nutrition. HH food insecurity is a problem specifically for displaced people [13]. Food insecurity happens when people are frequently concerned about accessing adequate amount of safe, affordable, and nutritious foods. Lack of income to meet the expenses of safe food can cause food insecurity [14].

Poor infant feeding behaviors, poor home care for ill children, and poor health-seeking behaviors are included in poor social and care environment [13, 15]. The social and care environment within the HH and local community also can directly influence malnutrition.

Infant and young child feeding practice is vital component of good nutrition and health. Appropriate childcare, which includes infant and young child feeding practices, is an essential element of good nutrition and health. Cultural factors and resources such as income, time and knowledge also influence caring practices as well as attitudes to modern health services, water supplies, and sanitation [13, 16].

Access to affordable health service, availability of safe water, adequate sanitation, and good housing condition are prerequisites for adequate nutrition [13, 15, 17]. Study conducted in different countries showed that poverty is the most important factor of malnutrition. In an area where poverty is prevalent, children do not obtain balanced diet [13].

2.3 Basic-level causes of malnutrition

The causes of malnutrition identified in UNCIEF conceptual framework on causes of malnutrition included potential resources and resources and control (human, economic, and organizational resources). However, a new conceptual framework developed by Young [6] to address acute malnutrition in Africa's dry lands encompasses: environment and seasonability, system, formal and informal institutions, and livelihood system. In this conceptual framework, system, formal and informal institutions included governance and political economy, food and health system, gender, cultural and social norms. Livelihood system comprises livelihood resources, strategies, and goals [6].

In basic causes, there are three essential parts of resources: human resource (people, knowledge, skill, and time), economic resource (assets, lands, income, and others), and organizational resources (formal and informal institutions, extended families, and child care organizations) [18].

The formal national institutions that make up the system of governance are centrally essential. It includes civic, political, and economic institutions. Informal institutions include markets, traditional institutions, and wider social customs and rules. These informal social systems determine power relations and resource distribution between different social groups in society, which in turn determine disaster risk and risk of malnutrition [6].

The basic causes of malnutrition are poverty, lack of information, political and economic insecurity, war, lack of resources at all levels, unequal status of women, and/or natural disasters [15].

2.4 Causes of malnutrition in children

Malnutrition in children is caused when the demand of nutrient and calories is deficient. Increased demand for nutrients and calories that may be deficient in a normal diet.

Preterm babies have more chance of becoming malnourished than other babies. Preterm babies are at a higher risk of malnutrition as are infants at the time of weaning. Congenital heart disease, childhood cancers, cystic fibrosis, and other long-term diseases are the major risk factors for malnutrition. Neglected children, orphans, and those living in care homes are prone to malnutrition [9]. Some children may become malnourished because of an eating disorder or a behavioral or psychological condition that means they avoid or refuse food.

2.5 Causes of overnutrition

The conceptual framework developed by UNCIEF and the new conceptual frame developed for dry lands of Africa focus on the causes of undernutrition. However, currently double burden of malnutrition became an international agenda. Therefore, dealing with causes of overnutrition is mandatory.

Energy overnutrition is common in developed countries. Sometimes, people with this type of overnutrition may also experience micronutrient undernutrition if their foods are high in calories but low in micronutrients.

There are many causes of overnutrition. Overnutrition is caused by consuming too much energy than a person needs every day. Consuming too much energy will causes weight gain over time unless a person increases physical activity. It does not matter if those extra calories come from macronutrients (fat, carbohydrates, or protein) because the body takes whatever it does not need and stores it as fat. Overnutrition is associated also with eating too much food and hence having an excessive intake of many nutrients rather than of a single one.

Types of malnutrition	Caused by deficiency of	Diseases and abnormal conditions caused by malnutrition
Protein energy malnutrition	Protein	Kwashiorkor
	Protein	Marasmus
Micronutrient deficiency	Iodine	Goiter
	Vitamin A	Bitot's spots, Night blindness
	Iron deficiency	Anemia
	Thiamine (Vitamin B1)	Beriberi
	Niacin (Vitamin B3)	Pellagra
	Folic Acid (Vitamin B9)	Several birth defects.
	Vitamin C (Ascorbic Acid)	Scurvy
	Vitamin D	Rickets, Muscle diseases, osteoporosis
	Vitamin E	Hemolytic anemia in premature infants and children
	Vitamin K	Abnormal blood clotting,
	Calcium	Osteoporosis, Osteomalacia,
	Zinc	Growth retardation
	Selenium	Keshan's disease
Overnutrition	Caused by consumption of over-energy and micronutrients	Cardiovascular disease. Cancer. Type II diabetes

Table 1.
Common malnutrition and their causes.

Consuming energy above 1587 Cal/day, protein above 41–57 g/day, and fat above 19–32 g/day increases overweight/obesity both in men and women [19].

Per-capita per day consumption of milk/milk products, fats, and oils (including meat and meat products), sugars and jiggery (including condiments, biscuits, *etc*.), and salts/sodium showed a significant dose-response relationship with overweight/obesity prevalence [19].

Micronutrient overnutrition occurs when a person consumes too much of any certain nutrients. It's possible to get too much of most vitamins or minerals, but usually this happens when you take mega doses of dietary supplements [20]. Micronutrient overnutrition can cause acute poisoning, such as taking too many iron pills at once [21]. Micronutrient overnutrition often results from the use of self-prescribed over-the-counter vitamin and mineral supplements. For example, it can also be chronic, taking large doses of vitamin B6 over several weeks or months [22].

The study also displayed that eating habit while watching television and not having close friend, educational status, sweet food preference, fat consumption more than 3 days per week, eating habit while reading and vigorous-intensity sports were associated with overnutrition [23].

2.6 Common malnutrition and their causes

The specific causes of malnutrition are different for different types of malnutrition. In **Table 1**, the common types of malnutrition, diseases, and their specific causes are described (**Table 1**).

3. Conclusion

Malnutrition is not getting enough energy or getting too much of nutrients. There are two forms of malnutrition: undernutrition and overnutrition. Malnutrition can be caused by various factors. The causes of malnutrition can be classified as immediate, underlying, and basic causes. Insufficient dietary intake and diseases can cause immediate malnutrition. HH food insecurity, inadequate social and care environment and insufficient health service, and unhealthy environment are classified in underlying causes of malnutrition. Basic-level causes of malnutrition include: potential resource and resource control, environmental factors, reasonability, system, institutions, and livelihood system.

Energy, vitamin, and mineral deficiency causes undernutrition. Overnutrition is caused by overconsumption of energy and micronutrients. Hence, there is double burden of malnutrition around world, great emphasis should be given for undernutrition and overnutrition. The causes of overnutrition are not clearly indicated in several studies. Therefore, studies that focus on cause of overnutrition should be done by including both developed and undeveloped countries.

3.1 Terminology

Anorexia: Persistent loss of appetite.

Beriberi: A degenerative disease of the nerves caused by a deficiency of the vitamin thiamine and marked by pain, inability to move, and swelling.

Condiments: A preparation (a sauce or relish or spice) to enhance flavor or enjoyment.

Crohn's disease: A serious chronic and progressive inflammation of the ileum producing frequent bouts of diarrhea with abdominal pain and nausea and fever and weight loss.

Cystic fibrosis: A genetic disorder, characterized by a tendency to develop chronic lung infections and an inability to absorb fats and other nutrients from food.

Dementia: Mental deterioration of organic or functional origin.

Dysphagia: Condition in which swallowing is difficult or painful.

Keshan's disease: A fatal heart disease found in children living in certain sections of China.

Osteomalacia: Abnormal softening of bones caused by deficiencies of phosphorus or calcium or vitamin D.

Osteoporosis: Abnormal loss of bony tissue resulting in fragile porous bones attributable to a lack of calcium; most common in postmenopausal women.

Pellagra: A disease caused by a dietary deficiency of niacin and marked by dermatitis, diarrhea, and disorder of the central nervous system.

Rickets: A disease, especially of children, caused by a deficiency in vitamin D that makes the bones become soft and prone to bending and structural change.

Scurvy: A disease caused by insufficient vitamin C, the symptoms of which include spongy gums, loosening of the teeth, and bleeding into the skin and mucous membranes.

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Chapter 2

Inflammation-Based Markers of Nutrition in Cancer Patients

Ogochukwu Izuegbuna

Abstract

Malnutrition and cachexia are common findings in cancer patients, and they predict poorer clinical outcomes. Close to half of cancer patients regardless of cancer type have malnutrition and will require one form of nutritional support either before or during treatment. The early identification of malnutrition is thus important to physicians and caregivers. The role of inflammation in the development and progression of malnutrition and cachexia is being unravelled. Increasing evidence shows that systemic inflammatory response and nutritional status are involved in tumour development and influence the clinical prognosis. Serum proteins such as albumin and prealbumin have traditionally been used by physicians to determine patient nutritional status. More recently, inflammation-based prognostic scores including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), C reactive protein-to-albumin ratio (CAR), prognostic nutritional index (PNI), Glasgow Prognostic Score (GPS) have shown promise and have begun to be used in clinical practice to predict prognosis of cancer patients. This chapter highlights the role and pathophysiology of inflammation-based markers in assessing malnutrition and cachexia and their relationship to clinical screening tools.

Keywords: inflammation, malnutrition, cachexia, cancer, nutrition screening

1. Introduction

Cancer is a major public health problem worldwide. It ranks as a leading cause of death along with cardiovascular disease (CVD). Cancer is the leading cause of death in 57 countries (including China), while CVD is the leading cause in 70 countries (including Brazil and India) [1]. In 23 other countries, it ranks either third or fourth. The GLOBOCAN 2020 report showed that there was approximately 19.3 million new cases and 10 million cancer deaths in 2020, thus making cancer the new challenge of the 21st century [2]. This increase in the number of cancer cases implies an increase in cancer-associated complications and morbidities. One such complication is malnutrition.

Cancer-related malnutrition is a broad term that encompasses complex poorly understood processes that are associated with specific types of cancers and their treatment protocols. Specific cancers such as oesophageal and pancreatic cancer are a high risk for malnutrition. Factors such as cancer-related symptoms (e.g. anorexia, early satiety, fatigue), treatment complications (eg, mucositis, nausea, taste changes), and psychologic distress all play a role and/or are risk factors in the development of malnutrition. Malnutrition is a common problem among cancer patients with high negative consequences. In cancer, it is associated with poor prognosis, reduced survival, increased therapy toxicity, reduced tolerance and compliance to treatments, and diminished response to antineoplastic drugs. Surveys done in the past showed a prevalence rate of between 25 and 70% with about 10–20% linked to malnutrition and not the malignancy itself. Malnutrition in cancer patients is distinctly different from malnutrition as a result of starvation, as the former arises from a combination of anorexia and metabolic dysregulation, caused by the tumour itself or by its treatment. Malnutrition when left untreated can progress to cachexia. Cachexia is defined as "a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment" [3]. The pathophysiology of cachexia has an underlying variable combination of reduced food intake and abnormal metabolism leading to a negative protein and energy balance. Cachexia is frequent in chronic diseases, and in cancer, it may account for about 20% of cancer deaths [4]. A diagnosis of cachexia is made in patients when the total body weight loss is >5% in the past six months (in the absence of starvation) or weight loss >2% in patients with body mass index (BMI) of <20 kg/m^2 [5]. Currently, cachexia is classified into three stages of clinical relevance, namely pre-cachexia, cachexia, and refractory cachexia [3]. Blum et al. defined pre-cachexia as weight loss >1 kg but <5% of usual body weight/6 months, but with an increased C- reactive protein (CRP) level and appetite loss, while refractory cachexia was weight loss >15% in the last 6 months + BMI < 23 kg/m^2 or weight loss >20% in the last 6 months + BMI <27 kg/m^2 [6]. If untreated, cancer cachexia would lead to a progressive functional loss, poor quality of life, chemotherapy-related toxicity, diminished response to antineoplastic treatments, and poor survival. At the refractory cachexia stage, the cancer is usually refractory to chemotherapy.

The relationship between malnutrition and the systemic inflammatory process is not a new one. Systemic inflammation is closely associated with weight loss and malnutrition in cancer [7–9]. Systemic inflammation has been fingered in the genesis and progression of malnutrition. It is known to affect important metabolic and neuroendocrine pathways as well as cause elevated energy expenditure at rest, decreased lean mass and reduced physical performance [10, 11]. Furthermore, cytokines especially tumour necrosis factor (TNF) alpha, interleukin (IL) 1 and IL-6 have been fingered in the induction of muscle wasting providing evidence for a link between malnutrition and inflammation. As aforementioned, systemic inflammation is thus a harbinger not only for malnutrition but for various comorbidities in cancer patients. Identification of cancer patients at risk of malnutrition is highly recommended. The PreMiO study highlighted the prevalence of malnutrition at the first visit by cancer patients [12]. The European Society for Clinical Nutrition and Metabolism (ESPEN) in its latest preoperative nutritional care assessment highlighted the degree of systemic inflammation among other things for individuals at nutritional risk [13]. Soeters et al. reinforced the urgency of including an assessment of inflammatory activity in the diagnosis of malnutrition [14]. Recent studies have shown that inflammatory models can be used to predict prognosis, as well as cancer-related malnutrition [15]. High level of systemic inflammatory factors which can facilitate tumour cell proliferation and metastasis are also known to be induced by malnutrition [16]. Thus, malnutrition can enhance a systemic inflammatory response. Control of inflammation in cancer can help modify poor nutritional status resulting in better response to therapy and improved survival. The early recognition of systemic inflammatory response should therefore be an integral part of nutritional management in cancer patients to improve short and long term outcomes.

2. Nutritional status

2.1 Prevalence of malnutrition in cancer patients

Malnutrition is a universal condition in cancer patients with grave clinical implications such as impaired quality of life, poor performance status, weight loss and cachexia. Studies from different countries across Europe shows a high prevalence of cancer-related malnutrition ranging from 25 to 70% based on nutritional assessments [17–19]. However, this differs across cancer types and stages of the disease [12, 20]. In the often-cited landmark study by Dewys et al., cancer type and treatment play a role in cancer-related malnutrition [21]. Tumour stage and age have also been noted as risk factors in malnutrition [22, 23]. In an epidemiological observation study, Pressoir et al. observed that pre-existing obesity (BMI ≥ 30), and Performance status ≥ 2 were associated with increased risk of malnutrition among cancer patients in 17 French Comprehensive Cancer Centres [19]. The Prevalence of Malnutrition in Oncology (PreMiO), a cross-sectional, observational study involving almost 2000 patients in 22 sites in Italy, revealed that 51.1% of treatment-naïve patients at their first visit to a medical oncology centre were already affected by a nutritional impairment, including risk for malnutrition (43%) and overt malnutrition (9%). Poor appetite was present in over 40% of cancer patients, with variable severity scores depending on the tumour type and stage of the disease, and ascribed mainly to early satiety, taste changes, and nausea [24].

The picture is not very different in developing countries. Pastore et al. in Brazil reported only 13.7% of lung and gastrointestinal cancer patients in a study were well-nourished [8]. Opanga et al. in Kenya reported that 33.8% of participants required critical nutrition care, 34. 8% symptoms management, 14.2% constant nutrition education and pharmacological intervention [25]. Ntekim et al. at Ibadan, Nigeria used nutritional screening assessment tools and reported a prevalence of 60% [26]. Children with cancer are also known to develop some form of malnutrition [27], however, the frequency may vary according to the type of cancer [28], and region [29, 30]. Brinksma, et al. reported the prevalence of malnutrition at diagnosis for developed countries, through a systematic review which included patients with different types of childhood cancer, aged from 0 to 18 years of age for acute leukaemias, the prevalence was 10%, 20–50% for neuroblastoma, and those classified as "other malignancies" was 0–30% [31]. This prevalence is lower than what is obtained in developing countries [28–30]. Villanueva et al. reported a prevalence of almost 50% [32]. Lemos et al. in Brazil reported that the prevalence of malnutrition is higher among paediatric patients with malignancies than in the general population though the difference was not significant [33]. These facts high- light the need for nutritional assessment in cancer patients regardless of age or region. Cancer patients should be assessed at several points during their management to identify aetiology and candidates that require nutritional support.

3. Pathophysiology

Cancer-related malnutrition can have profound negative effects on cancer patients' wellbeing and therapeutic outcomes. It usually results from local effects of a tumour, the host response to the tumour and anticancer therapies. Cancer cachexia which is a severe form of malnutrition is characterised by progressive weight loss, anorexia, asthenia, and anaemia. Cachexia is a poor prognostic sign, and is associated with reduced food intake and increased energy expenditure [34]. Cachexia also expresses itself as nutritional imbalances in a number of ways in cancer patients which include glucose intolerance and insulin resistance, loss of adipose tissue and lipolysis with increased fat oxidation rates [35], decreased lipogenesis, impaired lipid deposition and adipogenesis [36]. A decrease in protein synthesis and increase in protein degradation does occur in cancer cachexia [37] which is a key feature of skeletal muscle atrophy. Other features such as altered hormone levels [38], elevated cytokines [39, 40], increased insulin resistance [38], elevated synthesis of acute-phase proteins [34] and altered nutrient utilisation can be attributed to inflammatory mediators as well a host of other factors. Inflammatory markers have been implicated in all metabolic derangements in cancer-related malnutrition, and a better understanding of these markers with either the host or the tumour is necessary for better management of malnutrition and its complications.

3.1 Inflammation and cancer

Inflammation has been shown to play a major role in cancer development, progression and outcome and has been termed the seventh hallmark of cancer [41]. The observation of leukocytes within tumours by Rudolf Virchow in the 19th century gave a clue of a possible link between inflammation and cancer. This link is due to chronic inflammation which is mediated by pro-inflammatory cytokines, chemokines, adhesion molecules, and inflammatory enzymes with the promotion of all stages of tumorigenesis. Inflammation is the body's physiological response to tissue damage as a result of any pathological insult to the body's homeostasis. The body's inflammatory response can either be a resolution to the insult, or persistence of the insult in the form of chronic inflammation. Chronic inflammation can cause cellular changes and influence innate and adaptive immunity towards tumour growth. When this happens, an imbalance of pro-inflammatory and anti-inflammatory mediators can lead to cell mutation and injury creating an environment that is conducive to the development of cancer. This scenario holds for the onset of cancer but is important for the progression of the disease. Such progression is characterised by clinical signs and symptoms including nutritional impact symptoms and co-morbid metabolic abnormalities. This invariably leads to weight loss, chronic anaemia, wasting syndrome, fatigue with loss of quality of life. These symptoms are very prominent in cancer-related malnutrition. While multiple mechanisms can be associated with these symptoms, however, they are interrelated and the unifying factor is inflammation.

Inflammation is associated with tumorigenesis at every stage of its development including survival and metastasis [42]. On the other hand chronic inflammation is known to facilitate treatment resistance and this form of acquired resistance is a result of the production of cytokines, chemokines and growth factors by the tumour micro-environment rendering chemotherapy ineffective [43]. Besides, inflammatory responses can be induced by anti-cancer therapies [44, 45]. chronic inflammation is also known to worsen chemotoxicity [46]. A better understanding of the relationship between chronic inflammation and cancer can lead to the development of new strategies in the management of cancers as well as some of the complications such as malnutrition and chemotoxicity that arise during treatments.

3.2 Inflammation and malnutrition

A large number of cancer patients are known to show a form of cachexia syndrome which is characterised by anorexia, loss of adipose tissue and skeletal muscle mass. Most of these symptoms have been linked to inflammation. The Global Leadership Initiative on Malnutrition (GLIM) requires the combination of at least one phenotypic and one etiologic criterion is to establish the diagnosis of malnutrition. The phenotypic criteria include non-volitional weight loss, low body mass index, reduced muscle mass. In addition to this, etiologic criteria include reduced food intake or assimilation and disease burden/inflammatory condition [47].

Inflammation is so intertwined with the pathogenesis of malnutrition that the ESPEN recommended dividing malnutrition into disease-related malnutrition with and without inflammation [48]. For Disease-related malnutrition with inflammation, it is defined as underlying diseases causing inflammation with a consecutive lack of food intake or as uptake with a negative nutrient balance [49]. Inflammation is reported to have several metabolic effects. Cytokines such as IL-6, and TNF-α correlate with insulin resistance and appetite reduction and also cause inhibition of nutrients entering cells [5, 50]. Leptin, a 167 amino acid peptide and a member of the adipocytokine family plays a major role in body mass regulation and inflammatory/immune cells modulation. Diakowska et al. reported in a study of leptin and inflammatory markers in oesophageal cancer patients found that leptin correlated directly with BMI, TNF-alpha, albumin, and haemoglobin and indirectly with IL-6, IL-8, and hsCRP [51]. In a secondary analysis of the EFFORT trial by Merker et al., patients with high baseline inflammation (ie, CRP levels >10 mg/dL) were observed not to benefit from any form of nutritional support concerning the 30- day mortality [52]. However, this study was not tailored to cancer patients primarily. Wang et al. showed a clear association between high inflammation, clinical malnutrition and overall survival in patients with nasopharyngeal carcinoma [16]. These studies show that inflammation could be a key factor in cancer-related malnutrition. Inflammation is known to exert some effects on appetite and food intake, gastrointestinal functioning of the stomach and gut, among a host of other things [53]. These effects are mediated by circulating cytokines released as part of the systemic inflammatory response causing disease-related anorexia, decline in cognitive function, weight loss and anaemia. Thus, inflammation is an integral part of cancer-related malnutrition.

3.2.1 Cancer-related anaemia

Anaemia is a common problem in cancer patients. Anaemia prevalence is remarkably high and varies widely among cancer patients. It is estimated from various studies that between 30–90% of cancer patients had anaemia [54]. Anaemia is considered an indicator of poor nutrition and poor health especially through the malabsorption or non-utilisation of iron, folate, cobalamin and other micronutrients needed for the production of red blood cells. The prevalence is determined by the definition of anaemia. According to the World Health Organisation (WHO), normal Hb values are 12 g/dL in women, and 13 g/dL in men [55]. Maccio et al. reported a prevalence of 78.8% of anaemia in lung cancer patients [56]; Akinbami et al. reported a prevalence of 58% among breast cancer patients [57]. Anaemia is known to be associated with several co-morbidities including a decline in patients' performance status (PS), cognitive function, and decreased survival [56, 58]. While anaemia in cancer generally is known to have various aetiopathology, cancer-related anaemia (CRA) is believed to arise as a consequence of chronic inflammation.

Cancer-related anaemia (CRA) refers to a condition occurring without bleeding, haemolysis, neoplastic bone marrow infiltration, kidney and/or hepatic failure [59], and principally results from the chronic inflammation associated with advanced-stage cancer and the synthesis of pro-inflammatory cytokines by both immune and cancer cells. Unlike iron deficiency anaemia, CRA is typically normochromic (MCH >27 pg), normocytic (MCV between 80 and 100 fl), with a low reticulocyte count (<25,000/mL) and a low value of reticulocyte index (normal range between 1 and 2 which is a more accurate measure of the reticulocyte count corrected against the severity of anaemia based on haematocrit). In addition, it has normal/low serum iron concentrations (normal range 55–160 mg/dl for men and 40–155 mg/dl for women) and reduced total iron-binding capacity (transferrin saturation < 50%); ferritin values may be normal (30–500 ng/ml) or more often increased (>500 ng/mL), with increased iron storage [59]. The normal level of iron within the bone marrow reflects the body tacit handling of iron metabolism which is termed as "functional iron deficiency" which is also present in other types of anaemia associated with chronic inflammation. In addition, circulating levels of erythropoietin (EPO) is often not optimal for the level of anaemia thus presenting with also bone marrow hypoplasia. Adamson highlighted some of the pathogenetic mechanism of inflammation of chronic anaemia which includes: shortened erythrocyte survival in conjunction with increased erythrocyte destruction, suppressed erythropoiesis in bone marrow, effects of inflammation on erythropoietin production and alterations in iron metabolism that result in iron-restricted erythropoiesis induced by hepcidin increase [60]. According to Jain et al., the soluble transferrin receptor/log ferritin index can differentiate pure cases of anaemia of chronic disease from iron deficiency anaemia [61].

Like other types of anaemia in cancer, CRA has multifactorial pathophysiology with immune, nutritional and metabolic components affecting its severity. Many studies have demonstrated that inflammatory cytokines are a major contributor to the aetiopathogenesis of CRA. They achieve this through the derangement of various metabolic pathways including glucose metabolism, impairment of lipoprotein lipase, which controls the uptake of circulating triglycerides into adipocytes, and changing protein synthesis and degradation, with subsequent depletion in lean body mass [62]. In particular, proinflammatory cytokines like interleukin 1 and 6 released by cancer and activated immune cells in response to malignancy, may result in anaemia by inducing changes to iron balance, inhibition of erythropoiesis, impairment of EPO synthesis and activity, reduction of erythrocytes lifespan and changes of energy metabolism. IL-1 and TNF also induce the transcription factors GATA2 and nuclear factor-kB, both of which are negative regulators of the hypoxia-inducible factor 1 (HIF1) expression [63]. Reactive oxygen species (ROS) which are a major player in chronic inflammation are known to inhibit EPO synthesis by mimicking a false O2 signal in the renal peritubular interstitial cells. They equally inhibit erythroid precursor proliferation [64]. IL-6 regulates the synthesis of hepcidin, a 25 amino acid peptide made by the hepatocytes and involved in iron homeostasis by mediating the degradation of the iron export protein ferroportin 1, thereby inhibiting iron absorption from the small intestine and release of iron from macrophages.

The process of CRA is not an isolated one. It has been shown that malnutrition along with weight loss and reduced food intake is correlated with anaemia in patients with the chronic inflammatory disease [65]. CRA is therefore not a single condition, but associated with weight loss and remodelling of energy metabolism; thus CRA is a crossroad for both inflammation and nutritional status. Therefore management of CRA would involve not only anaemia but malnutrition as a whole.

3.2.2 Cancer-related anorexia and wasting

Anorexia can be defined as a loss of appetite associated with chronic illness in cancer patients and is associated with weight loss [66]. It is common in cancer patients and frequently associated with early satiety and taste changes. It occurs in half of the newly diagnosed cancer patients and up to 70% of patients with advanced disease. Cancer-related anorexia is an important clinical co-morbidity in cancer patients, and it harms nutritional status in advanced cancer. There are many causes of anorexia. They are classified as either being due to central or peripheral mechanisms. Peripheral causes include (i) tumours causing dysphagia or directly impinging on gastrointestinal function; (ii) tumours producing substances that alter food intake, e.g. lactate, tryptophan, or parathormone-related peptide; (iii) tumours leading to alterations in nutrients resulting in anorexia, e.g. zinc; or (iv) tumours producing inflammation leading to cytokine release. Alterations in gastrointestinal function can alter visceral receptor function, leading to altered secretion of gastrointestinal peptides, e.g. peptide tyrosine (PYY), and alterations in stomach emptying can alter feedback of satiating hormones. Peripherally, chemotherapy can alter taste perception and cause nausea, vomiting, mucositis, abdominal cramping, bleeding, and ileus [67]. Depression, pain, or a variety of alterations in central neurotransmitters are some of the central causes. Some centrally acting chemotherapy can also induce anorexia. For example, tamoxifen used in breast cancer treatment can inhibit fatty acid synthase in the hypothalamus, leading to an accumulation of malonyl coenzyme A (CoA). Increased malonyl CoA is associated with anorexia in cancer [68, 69]. The resultant effect of cancer-related anorexia is reduced caloric intake and alteration in nutrient metabolism with consequent loss of fat and lean mass.

Several studies have focused on the mechanisms underlying the metabolic changes observed in cancer-related anorexia and weight loss and some cytokines have been implicated including TNFα, IL-1, and IL-6 [70]. These cytokines are known to mimic leptin signalling and suppress orexigenic ghrelin and neuropeptide Y (NPY) signalling inducing sustained anorexia and weight loss. These cytokines are elevated in many cancers [71] and their chronic administration can induce anorexia and wasting [72, 73]. Interleukin 1 is produced by lymphocytes and macrophages and is a potent anorexigenic cytokine that is at least 1000-fold more effective than leptin [74]. IL-1 is reported to reduce the size, duration, and frequency of meals but does not reduce the desire for food [75]. It achieves this by the stimulation of corticotrophin-releasing factor (CRF) production by the hypothalamus [76]. TNFα is produced by monocytes, tissue macrophages and some tumours, and directly on the CNS to produce its anorectic effects by crossing the blood-brain barrier. An inhibitor of TNFα increased food intake in anorectic tumour-bearing rats [77].

Interferon-γ when administered centrally is known to reduce food intake and duration. Administration of TNF-α to laboratory animals induces a state of cachexia, with anorexia and depletion of adipose tissue and lean body mass [78]. Interleukin-6 is secreted by T-cells and macrophages as well as microglia, astrocytes, and neurons and has a well-established association with the onset of cachexia in both rodent and human wasting conditions [79]. While there are many mediators of anorexia in different disease states, IL-6 has been shown to regulate food intake and metabolism [80], signalling through neural gp130 receptors and even in non-cancer-related cachexia, plasma IL-6 is associated with the incidence of anorexia [81, 82].

Decreased caloric intake alone does not account for the profound weight loss observed in cancer patients. Metabolic abnormalities with subsequent elevation in basal energy expenditure are also contributing factors. Weight loss in cancer though affects both fat and lean mass, the latter seems more affected. In a study of 50 cancer patients by Cohn et al., Weight-losing cancer patients appeared to have lost both fat and lean tissue, but the loss of lean body tissue, particularly skeletal muscle, was the more striking feature [83]. This pattern is in contrast to starvation, in which fat is lost and lean tissue is better preserved. TNF-α, IL-1 and IL-6 have been shown to increase basal energy expenditure causing weight loss [84]. The muscle wasting that occurs in cancer is a result of a decrease in protein synthesis, an increase in protein degradation or a combination of both. These changes are attributed to the upregulation of inflammatory mediators, the activation of related transcription factors and signalling pathways, abnormalities in the expression of angiotensin II (Ang II), insulin-like growth factor-1 (IGF-1) and various receptors, proteins and kinases, and organelle dysfunction [85]. Muscle wasting thus occurs as a result of these processes.

4. Inflammatory markers of malnutrition

There are several clinical, biochemical and physiological indicators to diagnose malnutrition in cancer patients. One commonly used clinical indicator of malnutrition is the percentage of weight loss in a certain period. A weight loss of more than 5% in the previous month or more than 10% in the last 3–6 months is considered significant malnutrition. Other anthropometric measurements, such as body mass index (BMI), mid-arm circumference and mid-upper-arm muscle area can give information about the nutritional status and body composition of these patients. The ASPEN guidelines for diagnosing malnutrition, which looked at six characteristics that incorporate some of these clinical indices [86].

Biochemical markers which are sometimes indicative of inflammation are often used as markers of malnutrition. They include albumin, prealbumin, C-reactive protein, transferrin, total lymphocyte count etc. However, more recently, inflammation-based scores and ratios are being seen as more sensitive markers than the traditional ones [87, 88]. Other nutritional assessment tools use questionnaires incorporated with factors such as estimation of nutritional intake, laboratory parameters and calculation of unintentional weight loss. Such tools that have been used in cancer patients include the Prognostic Nutritional Index (PNI), the Nutritional Risk Screening 2002 (NRS 2002), the Controlling Nutritional Status (CONUT), Mini Nutrition Assessment (MNA), Malnutrition Screening Tool (MST), the Nutritional Risk Index (NRI) etc. [89]. In children with cancer, the Frisancho table is used to assess their nutritional status [29].

4.1 Albumin

Albumin is a serum hepatic protein with a half-life of 14–20 days. Albumin is the major carrier for many substances in the body, and also help maintain the body oncotic pressure. It enhances immunity, aids DNA synthesis as well as acts as an antioxidant [90, 91]. Due to its relatively long half-life and hepatic synthesis, it is seen as a good marker of malnutrition. However, albumin is a negative acute-phase protein, and its serum levels are down-regulated in response to inflammatory conditions and drugs especially those that affect the liver. Albumin is widely used as a marker of nutrition as well as a prognostic indicator of survival in cancer patients (though it is more of a marker for inflammatory response). Frutenicht et al. reported that albumin was a predictor of mortality in gastrointestinal tumour patients [92]. Das et al. reported that albumin was significantly correlated with Patient-Generated Subjective Global Assessment (PG-SGA) [93], thus hypoalbuminaemia is a marker of malnutrition. This was further affirmed by a study done on colorectal cancer patients where albumin was positively correlated with the MNA [94]. However, In a study of 74 cancer patients, Pastore et al. did not find significant variation between albumin and SGA [8]. In a recent study on 128 colorectal patients, at least two circulating cytokines (TNF-α and IL-10) affected the expression of serum albumin [95]. Albumin correlates with weight loss in cancer patients as well as with BMI. Albumin is equally incorporated into various indices such as the Glasgow prognostic score (GPS) and PNI. Albumin may not be the ideal marker for assessing malnutrition, but its incorporation into nutrition screening tools gives it a sense of validity.

4.2 C-reactive protein

CRP is the most common method used to assess the magnitude of systemic inflammatory response. Unlike albumin, it is a positive acute-phase protein. CRP is a prototype of short pentraxin present only in the pentameric form in plasma. It is synthesised by hepatocytes in response to trauma, inflammation and tissue damage. The synthesis of CRP is under the transcriptional control of cytokines and transcription factors. Interleukin-6 (IL-6) is the main inducer of CRP gene. CRP is associated with the development, progression and outcome of cancer [96]. In addition, some studies have found a positive association between altered CRP levels and weight loss in patients with cancer [97]. In a large international cohort of advanced cancer patients, Laird et al. reported that C-reactive protein was significantly associated with cognitive, physical, emotional and social functions as well as anorexia, pain and fatigue [98]. Yu et al. also observed a significant association between CRP and PG-SGA among patients with malignant tumours [99]. However, some other studies did not see any association between CRP and nutritional status [88, 92]. In a study done by Read et al., patients with advanced colorectal cancer were initially found to have a positive correlation between SGA and CRP. However, when two outliers were excluded, the association did not remain significant [100]. This observation may be a result of the effect of non-nutritional factors like cardiovascular disease and infections. CRP is positively correlated with weight loss, and negatively correlated with PNI. Like albumin, CRP is incorporated into some nutritional screening tools which give it some validity.

4.3 Inflammation scores

Traditional inflammatory markers like CRP and albumin have been shown to have some limitations in malnutrition diagnosis based on their low specificity. It has been muted that inflammation-based scores that combine CRP and albumin, such as the CRP/Albumin ratio (CAR), may have more significant prognostic value than each of these markers singly in malnutrition. These inflammation-based scores which include inflammatory ratios and indices, and haematological ratios have been reported to be associated with cancer progression and outcomes [101, 102].

The Glasgow prognostic score or modified Glasgow prognostic score indices which combine serum CRP and albumin levels have also been viewed as a prognostic indicator in many cancers. There have been more than 60 studies (>30,000 patients) that have examined and validated the use of the GPS or the modified GPS (mGPS) in a variety of cancer scenarios [103]. Silva et al. demonstrated the clinical utility of modified GPS in a palliative care setting and its association with SGA [104]. SGA was also strongly correlated with the Glasgow prognostic score in oesophageal cancer patients [105]. GPS currently serves an important significance as a nutritional marker in cancer.

The concept of the CRP/albumin ratio (CAR) was first proposed by Ranzani and demonstrated its value for the mortality of septic patients [106]. CAR unlike GPS is a continuous variable and is believed to have a wider clinical application than GPS. A high level of CAR is linked to survival in cancer patients [102, 107]. De Lima reported that CAR was significantly associated with weight loss and SGA in patients with gastrointestinal tumours [108]. A high preoperative CAR and low PNI strongly correlated with poor survival in pancreatic cancer [109]. In oral cancer patients, Park et al. showed that CAR was significantly associated with both PNI and mGPS, and was also a better marker for survival than the other markers [110]. Another related novel marker, CRP/Prealbumin ratio is seen as a prospective inflammatory nutritional prognostic tool in cancer [111], likewise the albumin/CRP ratio [8, 88].

Haematological test i.e. complete blood count is one of the most common, simple and accessible tests in cancer evaluation. As cellular markers of inflammation, they provide prognostic and treatment information about the cancer patient. It is now established that the presence of a pre-operative systemic inflammatory response is predictive of disease progression and poorer outcome, regardless of tumour stage, in patients with various cancers [112, 113]. Inflammation based scoring systems such as the modified Glasgow Prognostic Score (mGPS) and the Neutrophil-Lymphocyte ratio (NLR) have prognostic value in different solid tumours [112]. However, concerning the NLR, multiple thresholds have been used to define high and low NLR values and some have suggested that its prognostic value is mainly derived from the neutrophil count and that the lymphocyte count makes little contribution [114]. Platelets are known to shield tumour cells from shear forces and assault of NK cells, recruit myeloid cells by secretion of chemokines and mediate an arrest of the tumour cell platelet embolus at the vascular wall [115, 116], which indirectly makes the Platelet- lymphocyte ratio (PLR) a prognostic marker in cancer. Studies have revealed that combinations of these parameters could accurately predict the prognosis of a patient than a single index. Like with other inflammatory markers, haematological ratios are associated with malnutrition. Many studies have reported the relationship between NLR and nutritional status. In a recently published work, Siqueira et al. demonstrated the relationship between NLR and nutritional risk in some cancer patients [117]. Sato et al. equally reported a significant inverse relationship of prealbumin with NLR [118]. NLR was associated with SGA especially in severely malnourished cancer patients [119] as well as with percentage weight loss [92].

PLR is another haematological ratio and inflammation marker that has been reported to be associated with many conditions including cancers. Elevated PLR is associated with increased all-cause mortality in different conditions [120], is a prognostic marker in many cancers [121] and is also associated with nutritional status [122]. As a marker of nutrition, PLR was significantly correlated with PNI and BMI in pancreatic cancer patients [87]; along with NLR was significantly associated with PNI in hepatocellular carcinoma [123]. PLR is also associated with haemoglobin and post-op complications in colorectal cancer patients affecting morbidity rates [124]. Sarcopenia, characterised by a decline of skeletal muscle plus low muscle strength and/or physical performance was reported to be associated with NLR and PLR in both renal cell carcinoma and gastric cancer patients [125, 126]. In addition PLR significantly correlated with both BMI and haemoglobin [125]; while in the gastric cancer patients, both PLR and NLR were significantly associated with NRS, albumin, haemoglobin, and cancer stage [126]. NLR and PLR are also reported to be significantly associated with performance status in cancer [115]. The main shortcomings of the haematological ratios are the different cut off levels in various studies.

Some other haematological ratios and scores such as lymphocyte monocyte ratio (LMR), neutrophil platelet score (NPS) etc. have been reported to have some prognostic value in cancer [101]. The monocyte lymphocyte ratio (MLR) was reported to be significantly correlated to PNI and albumin [87] in pancreatic cancer making it a potential nutritional marker like NLR. Combination haematological indices such as the Combination of Platelet count and Neutrophil to Lymphocyte Ratio (COP-NLR), combination of neutrophil-lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) (CNP), fibrinogen and NLR (F-NLR) etc. have been shown to have good prognostic value, and their association with nutritional indices should broaden the nutrition/inflammation arena further.

4.4 Cytokines

Cytokines are protein molecules released by lymphocytes, monocytes/macrophages and mediate as well as regulate immunity, inflammation and haematopoiesis. Cytokines are the major players in cancer-associated malnutrition, being involved in every aspect of the pathophysiology as earlier explained. They hold great promise as inflammatory markers in nutrition, however, they pose some challenges, particularly their short half-lives [127, 128]. They can be measured in serum or plasma samples; however, measurements from the different sample types cannot be used interchangeably [129]. Tissues or supernatant from cultured peripheral blood mononuclear cell (PBMC) preparations can also be employed in their measurement. The effect of freezing and thawing can lead to its degradation affecting the measurement. There is an equal lack of standardisation of assays, and because cytokines affect multiple pathways, there is also a lack of specificity [130].

Despite its shortcomings, cytokines are still studied in nutrition research. IL-6 is incorporated into the newly validated CAchexia SCOre (CASCO) for staging cachexic cancer patients [131], although it is not included in the simplified MiniCASCO (MCASCO) [132]. IL-6 is also associated with weight loss, and also correlates with high Prognostic Inflammatory Nutritional Index [133, 134].

4.5 Other markers

Other inflammatory markers for measuring malnutrition include prealbumin, haemoglobin, transferrin, and absolute lymphocyte count (ALC). Many of them are incorporated into nutritional indices either as ratios or as scores. Prealbumin, haemoglobin and ALC are incorporated into the CASCO score [133]. For ALC, levels are associated with various degrees of malnutrition. Levels >2000 cells/m^3 (normal), 1200 to 2000 cells/m^3 (mild depletion), 800 to 1199 cells/m^3 (moderate depletion), and < 800 cells/m^3 (severe depletion) [135]. Haemoglobin is part of the haemoglobin platelet ratio (HPR) which has been shown to have diagnostic value in colon cancer [136].

5. Conclusion

As it has been shown, inflammation plays a central role in cancer-related malnutrition which can lead to cachexia and eventually death. Malnutrition accounts for about 20% of all cancer deaths and is associated with reduced quality of life. Markers of inflammation play a prognostic role in cancer and are most times significantly associated with indices of malnutrition in cancer patients. Several studies have shown that inflammatory markers can be used as a screening test for malnutrition in cancer; though their specificity may be below as a result of other disease states. The inflammation-based scores are more sensitive than the single tests. These tests are cheap and easy to apply. However, their major shortcomings are different cut off levels.

Conflict of interest

The author declare no conflict of interests.

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Chapter 3

Energy Metabolism and Balance

Luboš Sobotka

Abstract

Malnutrition is a typical consequence of a disturbed energy balance. The intake of energy substrates should meet the requirements of organism and reflect the ability to metabolize the received substrates in various clinical situations. That means that required energy intake is dependent not only on energy expenditure (measured as substrate oxidation during indirect calorimetry) but also on requirements of organism for growth, defense against infection, healing process, regeneration, and so on. Many malnourished patients experience a combination of stress and underfeeding. Both nutritional status and disease activity must be considered when nutritional support is required; this information is important for selection of energy substrates and prediction of suitable energy balance. Therefore, proper knowledge of energy metabolism principles is important as well as information about methods of energy expenditure measurement. During an acute catabolic phase, the energy balance should be neutral, because efficient anabolic reaction is not possible. However, after the acute condition has subsided, the undernourished subject should be in positive energy balance with the goal to ensure the restoration of original "healthy" condition. The period of positive energy balance should be long enough and combined with rehabilitation therapy and increased protein intake.

Keywords: energy, indirect calorimetry, energy expenditure, energy balance, energy metabolism

1. Introduction

Most energy substrates found in nature come from water and carbon dioxide. These simple molecules are used by plants wherein the energy of sunlight is transferred to the molecules ATP and NADPH, with oxygen being formed as a by-product [1]. Subsequently, carbon dioxide is fixed in the Calvin cycle, and glucose is synthetized using NADPH and ATP [2]. Carbohydrate molecules form a large part of the plant structure (especially cellulose and starch); at the same time, these molecules themselves are the basis for the molecules and energy substrates (e.g., fats and amino acids and proteins or vitamins) [3, 4].

Unlike plants, animals require energy intake in the form of energy substrates (sugars, fats, and proteins), which are primarily produced by plants. These substrates are used by organisms as building blocks for their own growth and development and are oxidized in the body to form carbon dioxide and water (the primary compounds, from which plants synthetize energy substrates). This fantastic cycle of dependence on the plant and animal kingdoms ensures stability and, gradually, development and results in the existence of countless plant and animal species that are constantly evolving and disappearing, with their energy laws and intermediate metabolism following very similar rules [3].

2. Energy metabolism

2.1 Energy phosphates

The universal way for energy transfer in all cells is the phosphorylation and dephosphorylation of some molecules [5]. These are mainly the adenosine diphosphate (ADP) and creatine (C) molecules that are phosphorylated to the ATP (adenosine triphosphate) and CP (creatine phosphate). However, only ATP can be termed as universal energy currency of all energy demanding processes in the cell and body [6]. The turnover of the ATP molecule is extremely high; it is about 100–150 moles per day in resting conditions. This corresponds to 50–75 kg of newly formed ATP per day. As the whole amount of ATP in the human body is much lower, the turnover of this ATP is extremely high. The ATP present in the human body is thus consumed and newly synthetized within 1–2 min, and constant ATP synthesis is thus an obligatory condition for living organisms [7]. In animals, this rapid ATP turnover is provided by constant oxidation processes in mitochondria and, to a lesser extent, pathways related to phosphate transfer from other metabolites (e.g., dephosphorylation of 1, 3-bisphosphoglycerate and phosphoenolpyruvate). Nevertheless, the oxidation of energy substrates in mitochondria is the main mechanism for ATP synthesis. The energy substrates are consumed in food as carbohydrates, lipids, and proteins.

2.2 Energy expenditure and energy intake

Knowledge of energy balance is very important for the management of malnutrition. Energy balance is composed of two parts:

1. Energy expenditure

2. Energy intake

Energy expenditure is a continual process that fluctuates only in intensity due to the constant presence of essential metabolic processes that require energy (such as cell division, protein synthesis and breakdown, neuronal function, membrane potential); thus, continual production of energy phosphates is essential for life [8]. Moreover, processes requiring more energy take place during physical activity and other conditions (such as increased body temperature and disease process). On the other hand, the intake of energy (food intake) is habitually an intermittent process. Thus, the energy substrates present in the food must be either directly oxidized, directly stored, or converted into substrates that are stored. When energy intake is low or absent, these stored substrates (especially lipids) are oxidized to create the energy necessary for survival [9]. In this way, the energy from the food must be either converted into ATP that is essential for ongoing metabolic and physiological processes or stored for period when energy intake is not ensured [10]. Moreover, certain part of the energy substrates that are absorbed in the gastrointestinal tract is utilized for systemic and local anabolic processes such as growth, regeneration, production of immune cells, and renewal of epithelial cells. In this way, energy metabolism and energy balance are not constant, but they change over days, months, and years depending on food intake, physical activity, growth, and health status [11].

The character of stored energy substrates is dependent on ingested food. After consumption of mixed diet, lipids (especially long-chain fatty acids) reach bloodstream as chylomicrons via lymphatic system and are directly stored in adipose tissue. On the other hand, carbohydrates are either used for non-oxidative purposes (reducing processes, synthesis of amino acids and nucleotides, etc.) or they are oxidized for energy production; a small part of absorbed carbohydrates is converted into fat [7]. Proteins and amino acids are usually utilized for synthesis of cellular components and body proteins; the excess of protein is oxidized as an energy source.

The tendency to accumulate energy is habitual and is mainly associated with increased fat intake and storage that leads to the development of obesity when energy balance is positive for a long time. Since a satisfactory food intake has not been constantly guaranteed in the wild, the amount of food eaten was greater than the immediate expenditure and fat calories were preferentially consumed to increase the energy reserves for period of fasting or famine [12]. Moreover, most animals (including humans) tend to increase their energy intake whenever there is possibility to eat. Due to energy reserves in fat tissue, a regular adult subject can survive 2 months of absolute fasting. In case of increased fat reserves, a person can survive a significantly longer period of starvation. For example, the ability to starve for more than 200 days has been described in very obese individuals in whom starvation has been used to control weight loss [13].

2.3 Methods of energy balance assessment

For effective monitoring of energy metabolism and consequently the energy balance of each individual, it is always necessary to know both their energy intake and energy expenditure [9].

2.4 Energy intake

The knowledge of intake of energy substrates (macronutrients), as well as the intake of other nutrients, is essential for the nutritional therapy of malnourished patients, as well as for their additional rehabilitation of patients. Thus, methods of energy intake monitoring are shortly described in the next part.

2.4.1 Monitoring of energy intake

Bomb calorimetry is a method used to accurately determine the amount of energy in individual foodstuffs. The food as well as not consumed part of servings is completely burned in a special device called a bomb calorimeter [14]. During the complete burning (oxidation) of food, the energy is released as heat that can be measured [15]. Moreover, both the amount of oxygen required for complete oxidation (burning) and the quantity of carbon dioxide produced are measured at the same time. However, it should be stressed that the amount of energy released from food oxidation in our body is lower than the amount of energy calculated from bomb calorimetry. This is because of several reasons:

- Some substrates are not oxidized in the body to the same extent as in a bomb calorimeter (e.g., nitrogen from proteins is excreted by kidney as urea that still contains a certain amount of energy, and some part of the energy is spent on urea synthesis).

- Other nutrients are not fully oxidized in the body (e.g., dietary fiber is not absorbed and oxidized and part of it is fermented by intestinal bacteria).

Bomb calorimetry is an effective research method; it is also useful for measurement of energy loss in the stool and thus to monitor the overall energy utilization of various food items. However, it is not practical for routine clinical practice.

Calculation of energy intake in foods based on their composition is a method to calculate the energy content in food. Calculation of energy in food items is based on their composition and amounts of basic macronutrients (carbohydrates, lipids, and proteins) that have a constant quantity of energy—see **Table 1**.

Using food tables and recognizing the composition of the individual food components and subsequently the whole meals from cooking recipes, it is possible to calculate the energy content of individual meals.

In addition to information about the composition of individual meals, the knowledge of the amount of the individual food items consumed during a particular time interval is essential. This can be achieved as follows:

- Weighing individual portions of food before consumption and then weighing any uneaten leftovers.

- Calculating the content of macronutrients and energy with the help of food tables.

This method is relatively accurate, but it is time and staff demanding (accurate weighing and calculation).

Quarter plate method is a method that can be used in institutionalized subjects (hospital and social care settings), where a standard diet is used [16].

- The content of energy and nutrients in the individual meals is defined in the hospital diet system.

- The nursing staff estimates the part of the portion that was consumed to the nearest one quarter of portion.

- The nutrient and energy eaten is obtained by multiplying the daily nutrient content by the average value of the proportion consumed.

Substrate	kcal/g	kJ/g
Carbohydrates	4.0	17
Lipids	9.0	37
Proteins	4.0	17
Alcohol	7.0	29

Table 1.
Energy content in the basic components of nutrition.

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Although the method is not as precise as weighing portions before and after meal, it is fast and useful for obtaining information on whether energy intake is sufficient. It immediately identifies a patient whose actual intake is low and in whom nutritional support is indicated [17].

2.4.2 Energy intake in free living subjects

We do not have any suitable, simple, and sufficiently accurate method for monitoring food intake for outpatients. At present time, two basic methods are used:

- ***Recording method***—the monitored person records the amount of all food consumed during some days (usually two working days and one weekend day). The amount of energy and other nutrients received is then calculated. Then, it is suggested that similar food intake is similar for the rest of time.

- ***Anamnestic methods***—the assessed individual should answer questions related to eating habits (e.g., How many times a week do you drink a glass of milk, eat a bowl of nuts, or eat a slice of bread?).

Both methods are used in epidemiological studies, but they are hampered by a relatively large error. Besides others, this is because some subjects tend to "adjust" the data according to optimal recommendations.

3. Energy expenditure

3.1 Indirect calorimetry

The oxidation of energy substrates is the largest part of energy production in animals. Complete oxidation of carbohydrates and lipids leads oxygen consumption (VO_2) and production of carbon dioxide (VCO_2) and water (H_2O). Complete oxidation of proteins is also associated with VO_2 and VCO_2; moreover, nitrogen is excreted in the urine in the form of urea. Therefore, VO_2 and VCO_2 and nitrogen excretion are equivalent to the energy expenditure and oxidation of individual energy substrates. The measurement of energy expenditure based on VO_2 and VCO_2 is called indirect calorimetry [18].

3.2 History

As early as the eighteenth century, Antoine Lavoisier discovered that animals produce heat. At the same time, Joseph Priestley described that the lives of experimental animals depend on the presence of oxygen, which is gradually consumed. These findings led to the conclusion that the energy metabolism of animals is identical to the burning process. In the nineteenth century, Carl von Voit and Max Joseph von Pettenkofer built a calorimeter to measure the differences in CO_2 production and O_2 consumption when consuming different foods. At the beginning of the twentieth century, Claude Gordon Douglas invented a bag into which exhaled air could be collected and subsequently analyzed. The great development of indirect calorimetry for the purpose of nutritional support of patients escalated after development of a ventilated plexiglass box to that the patient head could be placed by John

Kinney [19]. This allowed long-term monitoring of energy metabolism by indirect calorimetry [20].

3.3 Calculations

Substrate oxidation calculations obtained by indirect calorimetry are based on the stoichiometric equations of oxidation of basic energy substrates:

$$\begin{gathered}1 \text{ mol glucose} + 6 \text{ mol } O_2 \rightarrow 6 \text{ mol } H_2O + 6 \text{ mol } CO_2,\\ 1 \text{ mol palmitate} + 23 \text{ mol } O_2 \rightarrow 16 \text{ mol } H_2O + 16 \text{ mol } CO_2.\end{gathered} \quad (1)$$

The values of oxygen consumption and carbon dioxide production per 1 g of energy substrate are presented in **Table 2**.

Then:

Oxygen consumption:

$$VO_2 = 0.829 \text{ CHO} + 2.01 \text{ Fats} + 6.04 \text{ nitrogen in urine } [g]. \quad (2)$$

Carbon dioxide production:

$$VCO_2 = 0.829 \text{ CHO} + 1.43 \text{ Fats} + 4.84 \text{ nitrogen in urine } [g]. \quad (3)$$

Oxidation of energy substrates:

$$\begin{gathered}\text{CHO} = 4.59\ VCO_2 – 3.25\ VO_2 – 3.68 \text{ nitrogen in urine } [g],\\ \text{Fat} = 1.69\ VO_2 – 1.69\ VCO_2 – 1.72 \text{ nitrogen in urine } [g],\\ \text{Protein} = 6.25 \text{ urine nitrogen}.\end{gathered} \quad (4)$$

Total energy expenditure (EV):

$$EE = 3.87\ VO_2 + 1.19\ VCO_2 – 5.99\ N \text{ (total urine nitrogen in grams)}. \quad (5)$$

From the equations above, we can calculate both the total energy expenditure and the amount of oxidized carbohydrates, fats, and proteins from oxygen consumption, carbon dioxide production, and urinary nitrogen losses. Nitrogen loss has little effect on the results of energy expenditure calculated from VO_2 and VCO_2. Moreover, accurate measurement of nitrogen loss is difficult for clinical practice. Therefore, energy expenditure is routinely calculated from VO_2 and VCO_2:

Substrate	**O_2 consumption**	**CO_2 production**	**RQ**
	[l/g]	**[l/g]**	
Carbohydrates (glucose)	0.829	0.829	1.0
Fats (palmitate)	2.01	1.43	0.7
Protein (mixed protein)	0.966	0.774	0.8
RQ (respiratory quotient) = VCO_2/VO_2 1 g of nitrogen in urine = 6.25 oxidized proteins.			

Table 2.
Oxygen consumption and carbon dioxide production during complete oxidation of basic energy substrates.

$$EE = 3.84\ VO_2 + 1.12\ VCO_2\ \left(\text{Brouwer's formula}\right). \quad (6)$$

Other formulas for the calculation of energy expenditure can be found in the literature (Weir, Lusk, Elia), the constants of which differ according to the representation of individual substrates in the studies of individual authors [20, 21]. However, the overall impact of the different formulas is not significant for usual clinical practice.

Energy expenditure can also be measured by monitoring oxygen consumption alone or by monitoring carbon dioxide production alone.

Energy expenditure calculated from VO_2:

$$EE = VO_2\ (3.84 + 1.12\ RQ). \quad (7)$$

Energy expenditure calculated from VCO_2:

$$EV = VCO_2\ (1.12 + 3.84/RQ). \quad (8)$$

3.4 Double-labeled water method for energy expenditure measurement

The subject drinks water that contains a stable isotope of oxygen (^{18}O) and hydrogen (deuterium—^{2}H). Twelve hours after drinking this double-labeled water, the concentrations of ^{18}O and ^{2}H are measured in any body fluid (urine, saliva, or plasma). During the following observed period, both stable isotopes are eliminated from the organism differently:

- ^{2}H is excreted from the body only in the form of water.
- ^{18}O is excreted from the body both in the form of water and in the form of CO_2, as part of ^{18}O balances with the pool of plasma bicarbonate and is subsequently excreted by the lungs.

For this reason, the elimination rate of ^{18}O is greater than the elimination rate of ^{2}H. The difference between these values is equivalent to CO_2 production over the observed period. This method can be used in free living subjects for extended period. The optimal time interval is dependent on the metabolic rate. In very active individuals or newborns, it is 3–5 days, while in adults with minimal movement or the elderly, the measurement period is extended to 3–4 weeks [22]. The double-labeled water method has been used in numerous clinical studies or in extreme conditions (e.g., during the climbing to Mount Everest); however, due to high cost, it is not suitable for routine clinical practice.

3.5 Formulas used for calculation of energy expenditure

Resting energy expenditure (REE) is an individual's energy expenditure under resting conditions after 12 h of fasting. The value of this energy expenditure can be estimated from basic anthropometrical values (body height and weight), age, and sex. Several formulas have been proposed for REE calculation; the most used of these is still the Harris-Benedict formula which has been used for a hundred years [23]. A different calculation is used for women and men:

Women:

$$\begin{aligned} \text{REE} = {} & 655.0955 + (9.5634 \times \text{weight in kg}) + (1.8496 \times \text{height in cm}) \\ & -(4.6756 \times \text{age in years}). \end{aligned} \tag{9}$$

Men:

$$\begin{aligned} \text{REE} = {} & 66.473 + (13.7516 \times \text{weight in kg}) + (5.0033 \times \text{height in cm}) \\ & -(6.755 \times \text{age in years}). \end{aligned} \tag{10}$$

For quick orientation, it is possible to use a simple assumption that the basic energy expenditure corresponds to 1 kcal per 1 kg of body weight per hour; the daily basic energy expenditure can be calculated as:

$$\text{BEE} = 24\,x\ \text{body weight in kg}. \tag{11}$$

3.6 Components of total energy expenditure

Total energy expenditure (TEE) consists of three basic parts:

- Resting energy expenditure (REE)—this depends on body cell mass and represents energy expenses of the basic metabolic pathways, the activity of the heart and respiratory muscles, etc.

- Diet-induced thermogenesis (DIT)—10% increase in energy expenditure after food intake also called thermic effect of nutrition (TEN). This increase is due to energy spent for interconversion of metabolic substrates [24].

- Activity-induced energy expenditure (AEE)—the most variable component of the TEE that is dependent on physical activity. The activity associated with regular light work will increase energy expenditure by 50–70%. This increase can be doubled during physically demanding work or during sports activities [25].

During the stay in the hospital, especially in the intensive care unit, the values of energy expenditure can be modified according to **Table 3**.

3.7 Energy expenditure and nutritional support planning in malnourished patient

Knowledge of energy substrate oxidation and energy expenditure is still very important for research devoted to metabolism and nutrition. However, for routine planning nutritional support especially in malnourished subject the information about energy expenditure is not the most critical one. Knowledge of the goals of nutritional support is more important. If the goal of nutritional support is, for example, growth, regeneration, healing, or increase in muscle mass associated with rehabilitation, nutritional intake recommendations may differ by up to several tens of percent from the values measured by direct calorimetry. An example is a growing child for whom the recommended energy intake is up to twice the REE value or severely malnourished patient who needs extra 1000 kcal per day to gain 100 g of tissue.

EV is increased
• Fever 13% at 1°C,
• Tremor 100%,
• Visiting relatives 40%,
• Stressful breathing 25%,
• Nutrition 9%,
• Catecholamines 30%.
EV is reduced
• Hypothermia 13% at 1°C,
• Muscle relaxation 40%,
• Analgesia 50%,
• Adapted ventilation 20%,
• Starvation 10–20%,
• Beta blockers 25%.

Table 3.
Changes in energy expenditure during the stay in the intensive care unit [26].

Careful knowledge of nutritional goals and their monitoring during nutritional support is therefore far more important than accurate knowledge of energy expenditure. This issue will be further elaborated in the chapter devoted to the energy balance.

3.8 Energy balance and nutrition

In the early years of nutritional support (mostly parenteral), the prevailing theory was that catabolism associated with critical illness and subsequent malnutrition could be reversed by increased energy intake. Therefore, the goal of nutritional support was to increase energy intake to achieve positive energy balance. The so-called hypercaloric nutrition (or hyperalimentation) was used at that time [27].

However, with time this concept was proven to be wrong. Measurements of energy expenditure showed that elective operations do not considerably raise energy expenditure and that only patients with major trauma or very severe sepsis may show increased values by 20%–40% for a limited period [19]. In addition, the positive energy balance cannot reverse further catabolism caused by inflammation or injury in critically ill patients. An increase in skeletal muscle mass occurs only if the positive energy balance is combined with the corresponding physical activity [28].

Unfortunately, subsequently, we emptied the baby out with bath. As is the case, after finding out the above, the concept of hyperalimentation was criticized and abandoned altogether [29] and the concept of planned malnutrition was subsequently promoted in order to avoid the limited complications associated with a very positive energy balance. The problem is that the concept of a planned administration of a reduced energy dose can lead to a gradual loss of body cell mass (presented as muscle mass) of patients. This aggravates the malnutrition, and the patients are unable to leave the intensive care unit or hospital, or they die in subsequent healthcare facilities or even at home without achieving a tolerable quality of life.

As explained earlier, the human organism is very rarely found in a period of balanced energy balance. During the period of food intake, physical activity is usually limited and, conversely, during periods of maximum physical activity, food intake is limited [30]. Undoubtedly, the human body is able to very efficiently accumulate energy in the body's stores (especially fat) and use this energy during fasting or starvation. The fact that a healthy young person can fast for about 60 days demonstrates the human body's great ability to use accumulated energy [13, 31].

On the other side, the long period of negative energy balance always leads to the subsequent malnutrition and final exhaustion of the body. Protein stores are especially very important. When only 30–40% of the standard (original) protein content remains in the organism, there will be a resulting serious threat to life. Such losses occur in healthy individuals just after 50–70 days of uncomplicated starvation, when both adipose tissue and body proteins are lost from the body.

However, the ratio between the loss of adipose tissue and protein (especially muscle protein) depends on the inflammatory state of the body that significantly diminishes the ability to adapt to a negative energy balance. The loss of body protein is much faster during inflammatory disease than during uncomplicated starvation [32–34]. This is because systemic inflammation leads to an increase in the demand for amino acids for the purposes of the inflammatory response, which leads to a gradual loss of skeletal muscle proteins. For this reason, the length of survival of starvation during inflammatory conditions is significantly reduced. In addition, protein loss is associated with a consequent loss of bodily function and rehabilitation ability.

A common mistake is the fact that the supplied energy substrates (especially carbohydrates) are considered only as a source of energy, i.e., as those substrates that serve only to form ATP in the oxidation process [7]. However, these substrates have other and possibly more important functions for the organism; these substrates are needed as building blocks for growth and regeneration, for the reducing processes of the organism, for maintaining the internal environment, for defense against the invasion of microorganisms, for the transmission of nerve impulses, for communication between cells and organs, and the like [3]. Moreover, many energy substrates are lost from the body without being oxidized; these are, for example, energy losses in the stool but also losses in the form of other secretions or pus (originally formed by leukocytes) or peeled epithelium. For these reasons, the view of the needs of energy substrates for the organism must be more comprehensive. To satisfy all requirements, we cannot just follow the measurement of energy expenditure using indirect calorimetry, which reflects only one part of the energy substrates, namely the one that has been oxidized to water and carbon dioxide: see **Figure 1**.

The planned energy intake and subsequent energy balance of malnourished or sick individuals in need of nutritional treatment must always be in accordance with the goals of a comprehensive treatment strategy. For this reason, the selection of individual energy substrates is extremely important in patient with malnutrition. The goals of nutritional support must be well defined, and the total amount of energy along with the representation of individual energy substrates must be planned according to these goals.

3.9 Goals of nutritional support in terms of energy supply in malnourished subject

The optional intake of energy substrates or macronutrients is not constant and does not depend exclusively only on energy expenditure, measured by indirect calorimetry [35]. This is because indirect calorimetry summarizes only the actual quantity

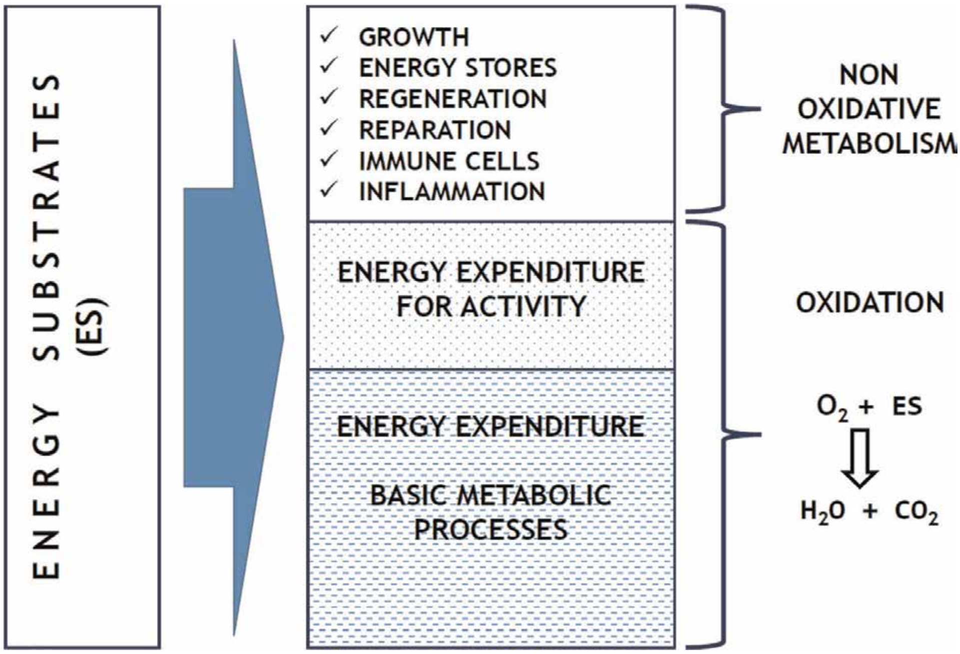

Figure 1.
Energy intake and oxidation—variable parts of the provided energy substrates are not oxidized.Reproduced with agreement of GALEN, authors, and editor in chief [27].

of energy substrates that are completely oxidized. The proposed intake of energy substrates and the resulting energy balance may vary according to the clinical conditions and the objectives of nutritional support:

- In stable individuals, the nutritional goal is to maintain or gradually improve bodily function and to prevent excessive weight loss (especially body cell mass).
- In undernourished individuals who have lost body and especially cell mass, the intake of macronutrients should guarantee the restoration of the normal composition of the body and its sufficient function.
- For growing children, energy intake must ensure normal growth and development.
- In severe and critical illness, when muscle anabolism is not possible, the intake of macronutrients should minimize the negative energy balance and associated muscle loss.
- After improvement in a critical condition or during postsurgical regeneration, the intake of energy substrates should guarantee the regeneration of tissue and function that were lost during the catabolic circumstances.
- For malnourished patients requiring early surgery, energy intake should ensure a safe surgical procedure and subsequent healing.

- In morbidly obese patients who are not in a critical or severe inflammatory state, the intake of energy should lead to a harmless decrease in fat mass without losing the functional potential of the body.

It is obvious that energy intake should not only cover energy expenditure, but also reflect the nutritional status of the patient, the clinical situation, and the goals of nutritional support. In malnourished subject, an intake of energy substrates must reflect not only resting energy expenditure but must also provide substrates for growth, regeneration, replenishment of cell mass and energy stores, and improvement in physical activity. On the other hand, a disproportionately high energy intake that does not correspond to the patient's clinical condition and nutritional goals is associated with accumulation of fat stores with all secondary metabolic changes [36].

Setting and satisfying nutritional goals is more important than the method of nutritional support (parenteral or enteral). If it is not possible to achieve these goals by oral or enteral nutrition, it is necessary to initiate supplementary or even complete parenteral nutrition.

3.10 Energy substrates during nutritional support

Regarding energy intake, it is necessary to address two aspects: the total amount of energy intake (how many calories or joules should be given) and the proportion of different substrates (carbohydrates, fats, and proteins) that provide this energy.

Energy intake depends on the goals of nutritional support:

- During acute or critical illness, provided energy should prevent or reduce the loss of body cell mass.

- During severe inflammation, nutritional support should also provide substrates necessary for inflammatory and immune processes.

- In severely malnourished patient, the nutritional support must guarantee the improvement in nutritional status, physical rehabilitation, and increase in skeletal muscle mass.

- Nutritional support should ensure or improve the growth of children.

Energy substrate intake should be also adapted to the following clinical condition:

- Critical illness

- Severe malnutrition

- Body composition (e.g., obesity)

Despite countless studies, it is still not easy to determine the exact energy intake required for an individual patient in a special condition. Moreover, metabolic conditions and energy needs change during the development of any disease. The goals of intake of energy substrates must also reflect the potential growth needs of the children and the recovery of body mass (i.e., muscle gains) in the depleted adult subjects during

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convalescence period. The adapting energy intake to individual circumstances requires careful patient monitoring and assessment of the effects of nutritional support.

3.11 Energy intake and phases of acute illness

Acute illness usually leads to negative energy balance that can result in deterioration of nutritional status and development of severe malnutrition. Therefore, nutritional treatment must be integral part of treatment. The intake of total energy and particular macronutrients is dependent on the stage of the disease and the nutritional status:

- ***Critically ill, hemodynamically unstable patients***—usually, stabilization of blood pressure and tissue perfusion is the priority of treatment at this stage. The spontaneous food intake is absent that leads to loss of body mass. However, nutritional support usually cannot reverse catabolism. Therefore, it is recommended not to exceed 25 kcal kg^{-1} h^{-1} until stable hemodynamic parameters have been established.

- ***Stable critically ill patients and patients during acute illness***—energy intake should be the same as energy expenditure. In these patients, energy expenditure is increased by disease-related factors, but decreased by immobility. However, achieving or exceeding these energy goals may not lead to a positive nitrogen balance or prevent further skeletal muscle loss. A negative nitrogen balance and subsequent loss of skeletal muscle are the results of malnutrition, inflammation, and immobilization. On the other hand, it should be emphasized that malnutrition in ICU patients for more than a few days can cause excessive protein loss and subsequent complications. Thus, after the improvement in the condition and the subsidence of inflammatory condition, the energy intake must be gradually increased to cover the needs for energy as well as synthetic processes in the organism.

- ***Convalescence phase***—at this stage, the body is already sensitive to increased energy intake and can use energy substrates not only for ATP production but also for anabolic processes, such as growth of children and restoration of lean body mass. Nutritional support should be introduced slowly to avoid refeeding syndrome, starting with 20–30% of the requirements and increasing to meet the full requirements within a few days. In order to restore lost tissue, the energy intake must be higher than energy expenditure and must be combined with higher intake of protein. At the same time, rehabilitation and mobilization must be initiated to ensure muscle anabolism. It takes time to regain muscle tissue (remember how difficult it is to gain muscle mass even in a healthy person). In addition to restoring lost tissue mass, there are also requirements for wound healing, synthesis, and proliferation of immune cells.

- ***Growing children and very malnourished patients***—in children and severely malnourished people after (e.g., after an acute illness), the energy intake must be higher than energy expenditure. However, as noted above, careful initiation of energy intake and careful monitoring of the clinical and biochemical status are essential in severely malnourished individuals to prevent the development of refeeding syndrome. During periods of positive energy balance and mixed food intake, carbohydrates are preferentially oxidized, while administered fat is stored in fat stores. The increased energy and protein intake must be combined with physical activity to optimize the rate of regeneration and gain of skeletal muscles.

4. Summary

- Energy requirements should be set in relation to the output but also to the patient's ability to metabolize the administered substrates.

- Most acutely ill patients experience a combination of stress and negative energy balance, which leads to the development of malnutrition.

- Majority of acutely ill patients, including ICU patients, have energy requirements that do not exceed 2400 kcal/day. During the acute catabolic phase, sepsis, or trauma, the goal of nutritional support should not be to induce a positive or zero nitrogen balance through increased energy intake.

- The main goal of nutrition in the acute phase of the disease should be to maintain function and reduce catabolism and progression of malnutrition.

- After the acute condition has subsided and during convalescence, nutritional support should treat disease-related malnutrition and restore the original condition.

- In severely malnourished patients, the period of positive energy balance must be extended and combined with rehabilitation therapy. At this stage, it is necessary to induce anabolism by increasing protein intake.

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Chapter 4

Malnutrition and Sarcopenia

Muneshige Shimizu and Kunihiro Sakuma

Abstract

Malnutrition caused by aging or disease can be defined as a state resulting from the lack of intake or uptake of nutrition, which leads to a change in body composition and the consequent impairment of physical and mental functions. Sarcopenia is a geriatric syndrome characterized by a progressive loss of skeletal muscle mass, strength, and performance. In this chapter, we (a) summarize the relationship between malnutrition and sarcopenia in various subjects, (b) review nutritional epidemiological evidence related to the prevention of sarcopenia, and (c) show evidence for the efficacy of nutrient supplementation in attenuating muscle atrophy in several patients. Malnutrition is closely related to severe sarcopenia, especially in older hospitalized adults, patients with chronic kidney disease (CKD), those undergoing hemodialysis, and those with cancer. Healthy diets (i.e., those ensuring a sufficient intake of beneficial foods, such as vegetables, fish, nuts, fruits, low-fat foods, and whole-grain products) are useful in preventing sarcopenia. The Mediterranean diet is a particularly healthy diet, but other diets, such as the healthy Nordic diet and traditional Asian diet, also help attenuate sarcopenia in older adults. Proteins, vitamins, minerals, and n-3 polyunsaturated fatty acids are important nutrients for patients with CKD, those on hemodialysis, and those with cancer.

Keywords: malnutrition, sarcopenia, diet quality, nutrients, muscle atrophy

1. Introduction

Adequate nutrition is important for all generations, especially the elderly, and is known to contribute significantly not only to maintaining good health and reducing the risk of chronic diseases but also to prevent future diseases [1–3]. The risk for malnutrition increases with age and is often attributed to inadequate recommended nutrient intake. Malnutrition in the elderly exacerbates their risk of developing several health problems and chronic diseases, such as sarcopenia and cardiovascular disease [4]. There is an ever-increasing need to implement nutritional screening as a method of routine health screening for older patients. Malnutrition in the elderly tends to be overlooked owing to physical and physiological changes associated with aging [5, 6]. There are three main approaches to nutritional assessment—the use of physiological and clinical indicators; a connection of physical measurements, motor skills, and cognitive status; and self-perception of health and nutrition [7].

The European Society for Clinical Nutrition and Metabolism (ESPEN) recommends that individuals at risk for malnutrition be identified using defined screening

Risk screening	At risk for malnutrition Use validated screening tools
Diagnostic assessment	Assessment criteria **Phenotypic** Non-volitional weight loss Low BMI Reduced muscle mass **Etiologic** Reduced food intake or assimilation Inflammation or disease burden
Diagnosis	Meets criteria foy malnutrition diagnosis Requires at least 1 phenotypic criterion and 1 etiologic criterion
Severity grading	Determine severity of malnutrition Severity determined based on phenotypic criterion

Table 1.
GLIM diagnostic scheme for screening, assessment, diagnosis and grading malnutrition.

tools. Moreover, the diagnosis of malnutrition should be made by a composite finding of either a low body mass index (BMI) value (<18.5 kg/m^2) or a low fat-free mass index, with BMI cutoffs for age, weight loss, and sex [8]. The Global Leadership Initiative on Malnutrition (GLIM) was formed by the world's leading clinical nutrition societies. A two-step approach was opted to diagnose malnutrition: first, screening to identify "at risk" conditions; and second, assessment to diagnose and grade the severity of malnutrition. Diagnostic assessment includes three phenotypic criteria (low BMI, nonvolitional weight loss, and decreased muscle weight) and two classifications by etiology (inflammation or disease burden and reduced food intake or assimilation) (**Table 1**).

Recently, Maeda et al. have reported the optimal BMI threshold for identifying severe malnutrition using the GLIM criteria and the prevalence of malnutrition by GLIM definition in clinical practice [9]. Patients with GLIM-defined malnutrition were found to exhibit significantly higher inpatient mortality compared to patients with adequate nutritional intake. On the contrary, Clark et al. compared the prevalence of and risk for malnutrition in patients admitted to a subacute geriatric rehabilitation facility using both GLIM and ESPEN criteria [10]. According to the GLIM criteria, approximately half of the elderly rehabilitation patients were malnourished. However, when the ESPEN definition was applied, the prevalence of malnutrition was found to be much lower. The authors suggest that various studies are needed to clarify the diagnostic accuracy of the GLIM and ESPEN criteria. Furthermore, overlap with syndromes such as cachexia and sarcopenia should be identified, and information dissemination and validation studies should be accelerated with the cooperation and support of nutrition-related professional societies.

2. Sarcopenia

Sarcopenia is defined as age-related loss of skeletal muscle mass, function, and strength [11]. Four years ago, the European Working Group on Sarcopenia in Older People (EWGSOP) revised the definition of sarcopenia [12]. The revised version proposed a simple decision tree for diagnosing sarcopenia (**Figure 1**). The most

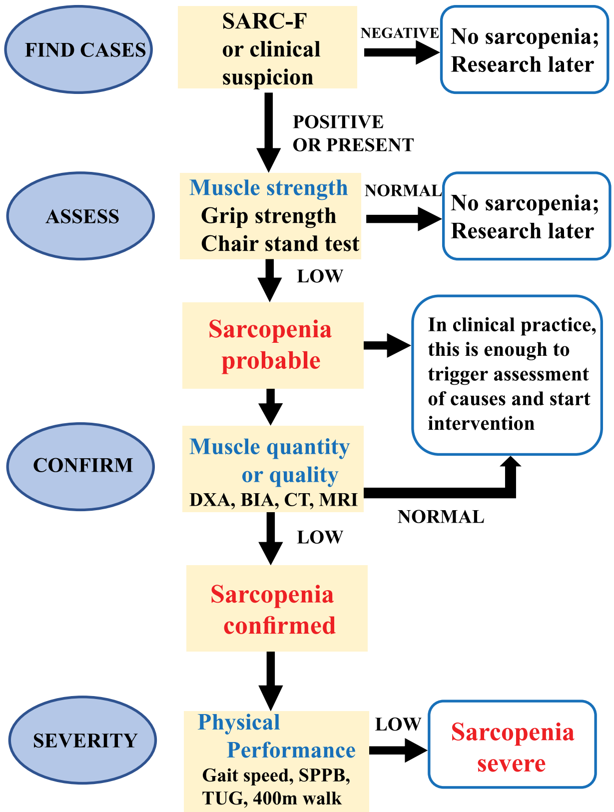

Figure 1.
Decision tree for the diagnosis of sarcopenia.

significant part of this revision is that muscle strength and function are the primary factors considered, which shows that they are more important than muscle mass [13].

Handgrip strength is used as an indicator of muscle strength. The simple and available methods of assessing physical ability contain the short physical performance battery and walking speed measurement that combines the get-up-and-go test, walking speed, and a balance measurement [14]. In addition, a sarcopenia-screening questionnaire is useful for patients over 65 years of age [15].

Approximate muscle weight can be estimated from simple measurements that calculate the corrected arm muscle area after measuring the skin thickness of the triceps skinfold thickness [16]. The bioimpedance method has the advantage of rapidly measuring lean body mass, but it cannot assess muscle volume directly. Data from dual-energy X-ray absorptiometry is typically utilized to calculate a skeletal muscle volume by correcting four limbs lean body mass by height or BMI [15, 17].

A remarkable decline in muscle strength (2.5%–3.0% per year) and mass (approximately 1% per year) has been reported in those over age 60 [18]. The prevalence of sarcopenia in people aged 65–70 years is 13–24%, and in those >80 years of age, it is >50% [19]. The prevalence of sarcopenia based on sex in individuals aged the 60s is 80% in women and 10% in men, whereas, in those >80 years of age, it is 18% in women and 40% in men [20].

Sarcopenia exerts major adverse effects on metabolism, function, mortality, and morbidity. The condition is associated with quality-of-life impairments, osteoporosis,

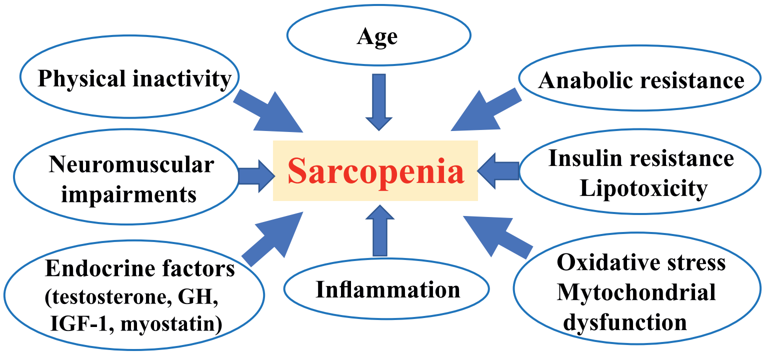

Figure 2.
Mechanisms underlying sarcopenia.

functional disabilities, falls, metabolic syndrome, cardiovascular disease, and other problems. Loss of both muscle function and muscle mass increases mortality by 3.7-fold [21] and increases the risk of falls by 2-fold [22].

The muscle is a biocontractile organ that enables movement by applying force to the bone. Muscle is essential for metabolic homeostasis because of its critical role in energy production, lipid oxidation, amino acid release, glycogen storage, and glucose uptake. In addition, muscle is indirectly involved in mediating immune responses and is also a reservoir of amino acids that can be used by immune cells and other cells. Although the molecular and cellular mechanisms of sarcopenia require clarification, certain common biological mechanisms, such as oxidative stress, mitochondrial dysfunction, hormonal regulation impairment, nutritional deficiency, and inflammation, have been suggested to be involved. Therefore, sarcopenia needs a multimodal management approach that combines nutrition, exercise, and anabolic and anti-inflammatory drugs (**Figure 2**).

3. Malnutrition and sarcopenia

The relationship between malnutrition and sarcopenia has been investigated in a range of subjects, particularly in studies published in the last 10 years, all of which concluded that malnutrition is strongly correlated with severe sarcopenia. We reviewed articles published after 2015, with a minimum of 67 subjects, that statistically revealed an association between malnutrition and sarcopenia (**Table 2**).

Dolores et al. investigated the association between malnutrition diagnosed according to the ESPEN and GLIM criteria and the development of severe sarcopenia/sarcopenia judged by the EWGSOP2 criteria [23]. In this study, 411 subjects were recruited, and their risk of developing severe sarcopenia/sarcopenia was assessed during the 4-year follow-up period. The results showed that those who were malnourished by the ESPEN definition had sarcopenia (adjusted hazard ratio of 4.28) and severe sarcopenia (adjusted hazard ratio of 3.86) and that those who were malnourished by the GLIM criteria had sarcopenia (adjusted hazard ratio of 3.23) and severe sarcopenia (adjusted hazard ratio of 2.87). The authors emphasized the importance of early action against malnutrition because it was shown to increase the risk of developing severe sarcopenia/sarcopenia two-fold during the 4-year follow-up.

Gerdien et al. summarized the association between sarcopenia and the prevalence of malnutrition in elderly hospitalized patients [24]. While reviewing seven studies

Reference	Population	Malnutrition prevalence	Sarcopenia prevalence	Findings
Dolores et al. [23]	411 community-dwelling heathy adults over 65 years old	7.3% (n = 30) by the ESPEN criteria, 23.4% (n = 96) by the GLIM criteria	3.9% (n = 16) by the European Working Group on Sarcopenia in Older people 2 criteria	Malnutrition was associated with an approximately fourfold higher risk of developing sarcopenia during 4-year follow up.
Gerdien et al. [24]	2506 older hospitalized adults	28.7% (n = 719) in malnourished, 47.2% (n = 1182) in risk of malnutrition	46.9% (n = 1175), including 41.6% (n = 1043) the overlapping prevalence of sarcopenia with malnutrition	The association between and prevalence of pre-frailty or sarcopenia and risk of malnutrition in older hospitalized adults in substantial.
Sato et al. [25]	77 ± 2 years in the older adults (n = 27) and 86 ± 4 years in the long-living older adults (n = 73)	Normal nutritional status in the older adults, nutritional risk in the long-loving older adults	45% (n = 45), most of these were from the long-living older adults (n = 38)	Older adults with malnutrition or at nutritional risk ran 13 times higher risk of sarcopenia.
Verstraeten et al. [26]	78–88 years in geriatric rehabilitation inpatients (n = 506)	51% (n = 257) by the GLIM criteria	49% (n = 250) in probable sarcopenia, 0.4% in confirmed sarcopenia (non-severe) (n = 2) and 19% (n = 94) in severe sarcopenia	23% had both malnutrition and probable sarcopenia, 0.2% had both malnutrition and confirmed sarcopenia (non-severe) and 13% had both malnutrition and severe sarcopenia.
Dolores et al. [27]	Older patients (84 ± 9 years) admitted to the post-acute geriatric care unit for functional loss resulted from a non-disabling medical disease (n = 88)	19.3% (n = 17) by the new ESPEN diagnostic criteria	37.5% (n = 33) in sarcopenia	The prevalence of sarcopenia was significantly higher in patients with malnutrition: 82.3% vs. 45.1%.
Beatriz et al. [28]	n = 339 sarcopenic primarily independent-living older adults, 85 ± 8 years	32.4% (n = 110) in the risk of malnutrition, 42.5% (n = 144) in malnutrition by the mini nutritional assessment	38.1% (n = 129) in sarcopenia, with a higher prevalence in women	The prevalence of malnutrition was statistically higher in individuals with sarcopenia compared with those without it.
Simone et al. [29]	n = 113 patients with CKD stages 3b-5, 80 ± 6 years	28% (n = 32) in the presence protein energy wasting syndrome	24% (n = 27) in sarcopenia	CKD sarcopenic patients were more malnourished than non-sarcopenic ones.

Reference	Population	Malnutrition prevalence	Sarcopenia prevalence	Findings
Catarina et al. [30]	n = 170 patients on hemodialysis, 71 ± 7 years	58.8% (n = 100) by the 7-point-subjective global assessment	35.3% (n = 60) in pre-sarcopenia, 14.1% (n = 24) in sarcopenia	The group with sarcopenia and malnutrition showed a higher hazard ratio 2.99 for mortality when compared to a group with no-sarcopenia and no-malnutrition.
Blauwhoff-Buskermolen et al. [31]	n = 67 patients with metastatic colorectal cancer, 66 ± 11 years	55% (n = 37) in overweight, 8% (n = 5) in obese, 57% (n = 38) in low skeletal muscle index	6.1% of skeletal muscle area decreased in 3 months by chemotherapy	Muscle loss of 9% or more during chemotherapy was associated with nutritional status and poor survival.

Table 2.
Summary of malnutrition and sarcopenia in various subjects.

(2506 patients), the researchers found a high association and overlap between sarcopenia and malnutrition. The results revealed that about half of the older hospitalized patients suffered from sarcopenia and malnutrition.

Sato et al. evaluated the prevalence and associated factors of sarcopenia in long-lived elderly people [25]. In this study, 100 eligible older adults were examined, and the mean age was 77.2 years in the elderly and 86.3 years in the long-lived elderly. The authors summarized that the risk of sarcopenia was 6 times higher in the elderly individuals >80 years of age and 13 times higher in the malnourished elderly individuals and those at risk for malnutrition.

Verstraeten et al. evaluated the prevalence of malnutrition and sarcopenia and the association between them in geriatric rehabilitation inpatients [26]. Out of the 506 geriatric rehabilitation inpatients, 51% were malnourished, 19% were severely sarcopenic, 49% were probably sarcopenic, and 0.4% were sarcopenic (nonsevere). Malnutrition with confirmed/severe sarcopenia and malnutrition with probable sarcopenia coexisted in 13% and 23% of the subjects, respectively. Almost half of the rehabilitation patients exhibited both malnutrition and sarcopenia.

Dolores et al. investigated malnutrition (diagnosed as per ESPEN) in elderly inpatients debilitated by acute illness and its connection to sarcopenia [27]. The 88 inpatients (mean age: 84.1 years, 62% women) with a BMI of <30 kg/m^2 were assessed with biochemical markers, and mini nutritional assessment strips were used to investigate the risk of malnutrition and sarcopenia. The results showed that the prevalence of malnutrition was 19.3% as per the ESPEN definitions. The prevalence of sarcopenia was 37.5%, of which 90.9% were malnutrition due to ESPEN, further indicating a strong association between the two.

Beatriz et al. investigated the association between sarcopenia diagnosis and nutritional status in nursing home residents [28]. This cross-sectional study included 339 elderly patients (mean age: 84.9 years, population: 64.3% women) in nursing homes, and their nutritional status was assessed using the ®Mini Nutritional Assessment. More than one-third of the residents had sarcopenia, and its prevalence was particularly high in women. Of the participants, 32.4% were at risk of malnutrition and 42.5% were malnourished. Rates of malnutrition were statistically higher in sarcopenia than in non-sarcopenia. Furthermore, the prevalence of malnutrition was the highest among those with reduced grip strength (62.8%) and in patients with severe sarcopenia (60.8%).

Simone et al. investigated the relationship of nutrition with sarcopenia, behavior, and inflammatory patterns in 113 older adults with advanced CKD [29]. Psychological and physical performance were assessed. The nutritional condition was evaluated by an inflammatory score for malnutrition, which also confirmed the presence of protein–energy wasting syndrome (PEW). The results demonstrated that 24% of the patients had sarcopenia. Patients with sarcopenia had relatively low creatinine clearance levels and low BMI values. Furthermore, patients with sarcopenia showed not only a higher prevalence of PEW (52% vs. 20%, $p < 0.0001$), but also a trend toward higher inflammation scores indicating malnutrition (6.6 vs. 4.5, $p = 0.09$).

Catarina et al. assessed the relationship of sarcopenia with malnutrition and nutrition-related markers, quality of life, and mortality in a cohort study of elderly patients undergoing chronic hemodialysis [30]. The subjects were 170 patients receiving hemodialysis for at least 3 months who were aged ≥60 years. Malnutrition, sarcopenia, and pre sarcopenia were found in 58.8%, 14.1%, and 35.3% of the patients, respectively. Patients with malnutrition and sarcopenia were older and showed significantly lower BMI, body fat, mid-arm muscle and calf circumferences, phage angle, and somatic cell mass. In addition, subjects with sarcopenia and malnutrition had a significantly higher hazard ratio for mortality (2.99) than those without these conditions.

Kiss et al. reported that all cancer patients are recommended to be screened for malnutrition and sarcopenia at the time of diagnosis or when clinical conditions change during treatment and recovery [31]. Malnutrition occurs with all cancer diagnoses, but certain cancers, such as neck and head, lung, and gastrointestinal cancers, exhibit up to a four-fold higher risk of malnutrition than breast cancer. In addition, Blauwhoff-Buskermolen et al. examined skeletal muscle changes during palliative chemotherapy in patients with metastatic colorectal cancer [32]. The muscle area of these patients decreased significantly by 6.1% during 3 months of chemotherapy. Additionally, patients who experienced a muscle loss of >9% during treatment had a significantly lower survival rate than those who faced a muscle loss of <9%.

4. Nutritional approach for the prevention of sarcopenia

The effects of diet quality on sarcopenia prevention in elderly individuals have been summarized as per the results of nutritional epidemiological studies. We reviewed epidemiological studies published since 2011 with at least 192 subjects that confirmed the impact of dietary quality on muscle function (**Table 3**).

Six studies have conducted human trials on the relationship between sarcopenia and diet quality (i.e., the intake of specific nutrients via food and/or the amount of nutrients consumed) [33–38].

Martin et al. explored the connection between physical ability (a short physical performance battery) and diet in the residents of West Hertfordshire [33]. Nutrient intakes were determined for the foods consumed using the manufacturer's composition data or the nutrients indicated in the UK National Food Composition Database. The preferred dietary patterns involved a high consumption of fish, shellfish, vegetables, and fruits but low consumption of sugar, fat, chips, and white bread. In women, the higher the dietary score, the greater the reduction in 3-min walking time and chair rise time. In addition, an inverse correlation was observed between

Reference	Population	Nutritional status	Physical function
Martin et al. [33]	n = 628 community-dwelling men (n = 348) and women (n = 280), 68 ± 3 years (men) 68 ± 3 years (women)	Administered FFQ pertaining to the 3-month period preceding the interview Data-driven: PCA. A "prudent" dietary pattern was identified.	In women, a higher prudent diet score was associated with a shorter 3-m walk time, shorter chair-rise time, and better balance.
Bollwein et al. [34]	n = 192 community-dwelling men and women, 83 ± 4 years	Administered FFQ of the German part of the EPIC study. Dietary indices: Adherence to a Mediterranean dietary pattern was assessed using the MED score	A relationship was observed between a high MED score and lower risk of a slow walking speed.
Granic et al. [35]	n = 791 men (n = 302) and women (n = 489), living either at home or in a care facility, 69 ± 0.3 years	Three dietary patterns were identified. (a) DP1, High Red Meat (b) DP2, Low Meat (c) DP3, High Butter	Men in DP1 had worse overall hand grip strength and slower timed up and go than those in DP2. Women in DP3 had slower timed up and go than those in DP2. Men in DP3 had a steeper decline in hand grip strength than those in DP1.
Perälä et al. [36]	n = 1072 participants, elderly men and women, 61 ± 0.2 years	Dietary indices: The *a priori*-defined Nordic diet score (NDS) was calculated as a measure of a healthy Nordic diet.	Women in the highest fourth of the NDS had a 5-point higher Senior Fitness Test score on average than those in the lowest fourth.
Suthutvoravut et al. [37]	n = 1241 community-dwelling men (n = 646) and women (n = 595), 75 ± 6 years	Three dietary patterns were identified. (a) DP1, high factor loading for fish, tofu, vegetables, and fruits (b) DP2, high factor loading for fish, rice, and miso soup (c) DP3, high factor loading for noodles	Men with the lowest tertile of the DP1 score had a higher likelihood of being sarcopenic. Women with the lowest tertile of the DP2 score had a moderate likelihood of being sarcopenic.
Davis et al. [38]	n = 552 men from the baseline and 15-year follow-up of the Geelong Osteoporisis Study	FFQ data were used to calculate the ARFS and the DIIscores. The ARFS is validated diet quality index. The DIIscore measures dietary inflammatory potential.	An anti-inflammatory diet and higher scores on a traditional dietary pattern both predicted greater skeletal mass index, while a pro-inflammatory diet predicted slower the timed up-and-go test.

Table 3.
Summary of nutritional epidemiological studies on the diet of quality in preventing sarcopenia.

the intake of vegetables, white fish, and shellfish and physical function. These findings indicated the presence of a relationship between diet quality and physical function in elderly women.

Bollwein et al. investigated whether the risk for frailty was lowered in subjects with higher Mediterranean diet (MED) consumption scores [34]. This score replaces the MED score proposed by Fung et al. [39]. The basic MED score introduced by Trichopoulou et al. was utilized [40]. The authors found that the MED score and walking speed were inversely correlated. Additionally, they observed a strong correlation between slow walking speed and good diet quality (high in vegetables, legumes, fruit, unrefined cereals, nuts, and fish) in aging people.

Granic et al. summarized the correlation between diet and decline in muscle power and physical performance in elderly people [35]. The study followed 791 elderly people for 5 years and detected changes in the Timed Up and Go test (TUG) scores and grip strength. Dietary intake was entered in a Microsoft Access dietary data system based on unique food codes (2000 above) and 118 additional categories by food groups based on the McCance and Widdowson food composition [40, 41]. The participants were divided into dietary pattern 1 (DP1—high in red meat), dietary pattern 2 (DP2—low in meat), and dietary pattern 3 (DP3—high in butter) based on the results of the dietary survey. The results showed that men with DP1 had decreased grip strength, and men with DP3 had a steeper decrease in grip strength than men with DP2. Furthermore, the TUG scores were significantly higher in DP1 men and DP3 women than in DP2 men and women. The results, therefore, suggested that a diet high in potatoes, red meat, butter, and gravy may exert a negative effect on physical performance and muscle strength in older adults.

Perälä et al. focused on the healthy Nordic diet and studied whether it was associated with improved physical performance indicators [36]. The 1072 subjects (mean age of 67 years) were investigated using the 128-item food frequency questionnaire (FFQ), after which an *a priori* Nordic diet score was derived. Physical ability was assessed using the Senior Fitness Test (SFT). The results of the SFT score showed that in women with the highest dietary score, the walking ability was improved by 17%, arm curl by 16%, and chair stand by 20% compared with women with the lowest dietary score. These results were considered meaningful evidence that women consume the healthy Nordic diet, which is based on fruits and berries (berries, pears, and apples), vegetables (lettuce, tomatoes, cabbages, lettuce, roots, roots, and legumes), cereals (oats, rye, and barley), low-fat milk (fat-free milk and milk with fat content <2%), and fish (Baltic herring, salmon), exhibit improved physical performance (upper and lower body muscular strength and aerobic endurance) after 10 years.

Suthutvoravut et al. studied the dietary contents and the development of sarcopenia in community-dwelling elderly Japanese people [37]. The subjects included 1241 individuals aged over 65 years who were not undergoing long-term medical treatment. The participants' diets were assessed using a simple descriptive dietary questionnaire. The dietary contents were surveyed by both Principal Component Analysis and Japanese dietary scores (fish, vegetables, fruits, soy products, mushrooms, pickles, and seaweed). The participants were categorized into dietary pattern 1 (DP1—typical Japanese diet, with high factor loadings for fish, fruits, vegetables, and tofu), dietary pattern 2 (DP2—high-factor loadings for rice, miso soup, and fish), and dietary pattern 3 (DP3: high factor loadings for noodles). The results suggest that men with the lowest DP1 are more likely to develop sarcopenia, and women with the lowest DP2 are moderately likely to develop sarcopenia. Furthermore, the findings alluded that low adherence to the Japanese dietary pattern, which comprises rice, fish, miso soup, tofu, vegetables, and fruits, was associated with a high prevalence of sarcopenia, regardless of sex.

Davis et al. investigated the alterations in the skeletal muscle mass and muscle function due to diet quality and dietary patterns over a 15-year period in 522 men [38]. The dietary survey was extracted from an FFQ and calculated the Australian Recommended Food Score and the Inflammation Index. Three dietary patterns were characterized—plant-based, Western, and traditional (Anglo–Australian). Higher scores in an anti-inflammatory diet rich in protein and vegetables predicted greater skeletal muscle mass, whereas the inflammatory diet was associated with lower TUG scores during the 15-year period. These associations were also significant when adjusted for the confounding variables.

Nutrition is an important factor that regulates muscle mass and muscle function and developing effective nutritional strategies to reduce muscle loss in several diseases warrants further studies. A few studies that have assessed the efficacy of nutritional interventions have been discussed below.

Kishimoto et al. demonstrated the changes in nutritional status and outcomes in adult stroke patients admitted for rehabilitation [41]. The 134 enrolled patients were divided into two categories—those with improved or normal nutritional conditions and those with poor or reduced nutritional status. Functional recovery was better in the category with improved nutritional status than that in the other categories. The authors concluded that improved or maintained nutritional condition was correlated with improved functional recovery in the rehabilitation of adult patients with stroke.

Patients with CKD are known to have a high prevalence of protein–energy malnutrition; hence, it is necessary to meet the patient's energy requirements and maintain the nitrogen balance to avoid the extra breakdown of muscle protein. Hoshino reported that a dietary protein intake of 1.0–1.2 g/kg/day, which is 1.2 times higher than that recommended for healthy individuals, is advised for patients with CKD [42]. In addition to the protein intake, an energy intake of 30–35 kcal/kg/day is necessary because the estimated energy leak during dialysis is approximately 300 kcal. Furthermore, an adequate intake of vitamins and minerals, such as vitamin D and iron, is essential to prevent protein catabolism.

Kiebalo et al. summarized the recommendations of the Society of Nephrology regarding the nutritional intake for dialysis patients [43]. The Polycystic Kidney Disease (PKD) Foundation has set the daily protein recommendation at 1.2–1.4 g/kg/day, slightly higher than the European guideline of 1.0–1.2 g/kg/day. The Foundation further suggests a daily calcium intake of 1000 mg and up to 3000 mg of sodium per day. For dietary phosphorus, the Kidney Disease Improving Global Outcome states that the daily intake should not exceed 4000 mg, which includes mineral as well as protein.

Ford et al. investigated the appropriate amount of dietary protein for preventing or treating skeletal muscle mass loss in cancer patients [44]. 40 patients with diagnosed stage II–IV colorectal cancer who were to receive chemotherapy were randomly assigned to a 12-week high-protein (HP) or normal-protein (NP) diet, with the HP group receiving 2.0 g/kg/day and the NP group receiving 1.0 g/kg/day of protein. The energy recommendations were based on the measured energy expenditure. The results showed that changes in skeletal muscle mass and physical functional muscle strength were higher in the HP group than that in the NP group, suggesting the importance of protein intake in cancer patients.

Schueren et al. published a systematic review of randomized trials using high-energy oral nutraceuticals (ONS) or ONS fortified with protein and n-3 polyunsaturated fatty acids to modulate cancer-related metabolic changes [45]. Interventions fortified with protein diets (i.e., an extra 32–33 g/day) and n-3 polyunsaturated fatty acids (i.e., an extra 2.0–2.2 g/day) of eicosapentaenoic acid) were observed to significantly improve cancer-related markers compared with the isocaloric controls.

Malnutrition during cancer chemotherapy is a factor associated with delayed disease improvement. Many investigations have been conducted on nutritional interventions during cancer treatment, but the evidence is highly limited. Hence, there is a need for further research to establish the desired timing and duration of nutritional intake and the know-how necessary for continuous nutritional intake.

5. Conclusions

In this chapter, we have summarized the relationship between malnutrition and sarcopenia in various subjects, reviewed the nutritional epidemiological evidence related to preventing sarcopenia, and showed data on the efficacy of nutrient intake in attenuating muscle atrophy in several patients. Malnutrition is closely related to severe sarcopenia, especially in older hospitalized adults, geriatric rehabilitation inpatients, patients with CKD, those undergoing hemodialysis, and those with cancer. An appropriate quality diet pattern (i.e., one that provides an adequate intake of beneficial foods, such as low-fat foods, fish, vegetables, fruits, nuts, and whole-grain products) is effective in preventing sarcopenia. The MED is a particularly popular healthy diet, but other diets of appropriate quality, such as a healthy Nordic diet or a traditional Asian diet, are useful in preventing sarcopenia in older adults worldwide. Proteins, vitamins, minerals, and n-3 polyunsaturated fatty acids are key nutrients for patients with CKD, those undergoing hemodialysis, and those with cancer. Further high-quality studies with large sample sizes, isocaloric placebo supplementation, and controlled diet quality are needed to clearly understand the effect of nutrient dose and duration on the prevention of malnutrition and sarcopenia.

Conflict of interest

The authors declare no conflict of interest.

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Chapter 5

Perspective Chapter: Crop Biofortification – A Key Determinant towards Fighting Micronutrient Malnutrition in Northern Ghana

Addison Baajen Konlan, Isaac Assumang and Vincent Abe-Inge

Abstract

Globally, more than 2 billion people suffer from iron (Fe), zinc (Zn), calcium (Ca), and other micronutrient deficiencies. In Sub-Saharan Africa, these micronutrient deficiencies are responsible for 1.5–12% of the total Disability Adjusted Life Years (DALYs). Ironically, these deficiencies often lead to invisible health conditions thus not often recognized in most low- and middle-income countries in terms of nutrition interventions to curb this anomaly. Therefore, there are alarming levels of iron deficiency in some Sub-Saharan countries like Ghana, which affects more than half of the female population. In the Northern part of Ghana, where the level of micronutrient malnutrition is high, some common staples including maize, millet, rice, and beans contain very low amounts of micronutrient. Biofortification is a novel nutrition-specific intervention that has proven to be an effective way to supply these micronutrients through the staples available whiles reducing the cases of micronutrient deficiency. This review aims to assess the potential role of biofortification in the prevention of micronutrient malnutrition in Northern Ghana. A thorough search of available data on the topic was conducted using Google Scholar, PUBMED, and ScienceDirect. Articles were accepted for review after thorough screening. Biofortification was found to have an effective potential in preventing micronutrient malnutrition in Northern Ghana. In conclusion, the incorporation of the three main types of biofortification in the Northern region of Ghana can enhance the production of food crops with adequate nutritional content that can improve the health status of the people in the region.

Keywords: micronutrient malnutrition, biofortification, Northern Ghana, nutrient-sensitive, nutrient-specific

1. Introduction

Malnutrition remains a big challenge in most developing countries most especially, in Sub-Saharan Africa (SSA) with children most affected. Fifty percent of all childhood deaths worldwide occur because of this challenge [1]. Globally, more than 2 billion people, representing one-third of the world population, are deficient in one or more mineral elements [2, 3]. The problem is very serious in low and middle-income countries, especially in Africa where the approximated risk for micronutrient deficiency is high for Ca (54% of the continental population), Zn (40%), Se (28%), I (19%) and Fe (5%) [4]. Lack of micronutrients in one's diet can lead to dire but often-invisible health problems, especially among women and young children [5]: this is often referred to as micronutrient malnutrition or 'hidden hunger. Hidden hunger hinders children and adolescents' mental and physical development and can lead to lower intelligent quotient (IQ), stunting, and blindness; women and children are the most affected [6]. In countries like DR Congo, Ghana, Mali, Senegal, and Togo, there are alarming numbers of iron deficiency anemia (IDA), which affects more than half of the female population [5].

In the past few years, Ghana has made significant progress in fighting malnutrition. Among few other Sub-Saharan African countries, they achieved their millennium development goals (MDGs) targets on stunting, wasting, and underweight in 2015 [7]. Nevertheless, they are yet to achieve their main target of bridging the nutritional and socioeconomic gaps between the Northern and Southern parts of Ghana, where the rate of malnutrition continues to be a challenge [8].

In Ghana's Northern, Upper East, and Upper West regions, malnutrition remains a major challenge. Based on statistics, children between the ages of 0–59 months in the three regions, found 18.4% of them being underweight, 11% having wasting, and 36.1% being stunted, as of 2012 [8, 9]. Meanwhile, nationally, based on statistics, 11% are underweight, 19% stunting, 5% wasting respectively [10]. Furthermore, the 2016 UN Global Nutrition report indicated that over $2.6 billion is lost annually in Ghana due to poor nutrition in children.

Vitamin A deficiency affects about 20% of children in Ghana with a higher prevalence in Ghana's Northern belt (31%) and lowers among children living in wealthier households (9%) [10].

Furthermore, according to the 2017 Ghana Micronutrient Survey, anemia was markedly high in the Northern belt (53.2%) compared to the middle (28.2%) and southern (32.3%) belts. A similar disparity was seen with iron deficiency and IDA as the prevalence in the Northern belt was significantly higher than in the other belts of Ghana [10]. According to [10], IDA was approximately 30% in the northern belt and below 8% in the middle and southern belts. Another data from [10] recorded that, 35% of anemic children had a severe iron deficiency, which is quite above the 28% estimate in a meta-analysis for Sub-Saharan African countries. This implies that Iron deficiency continually increases the rate of anemia among children in Ghana.

In a cross-sectional study that was conducted by [11, 12], 500 healthy blood donors were carefully chosen from three topographically varied regions in Ghana. They ranged in age from 17 to 55 years. They were 27.97 and 8.87 years old on average. The overall vitamin D deficiency rate was 43.6%. However, 41.2% , 45.3%, and 45.7% were discovered to be vitamin D deficient in the Northern, Middle, and Southern Sectors, respectively.

For the past years, several traditional interventions of reducing micronutrient malnutrition in Ghana, and most especially, in the Northern part of Ghana have been performed. They are iron-folic acid supplementation, vitamin A supplementation, fortification of flour and oil, complementary feeding, and exclusive breastfeeding [1]. The majority of these methods have principally reduced the morbidity and mortality of micronutrient malnutrition worldwide [13]. Nonetheless, these intervention strategies require more infrastructure, purchasing power, or access to markets and healthcare systems for their triumph [13]. It is often not available to people living in remote rural areas because of inconsistency in funding. Beyond doubt, money spent on these interventions is money well spent, both intervention strategies depend on uninterrupted funding. However, in some instances, funding can change, making it difficult to control micronutrient malnutrition. In the Northern part of Ghana, most diets are often low in diversity and dominated by staple crops such as maize, rice, cassava, sorghum, millet, and sweet potato. Such diets have an insufficient amount of micronutrients (minerals and vitamins) and hence leading to the increase in micronutrient deficiencies when consumed [14].

Micronutrient malnutrition, also known as 'hidden hunger, can be assuaged by direct (nutrition-specific) and indirect (nutrition-sensitive) intermediacies [15]. Nutrition-specific interventions center on consumption behavior and include dietary diversification, micronutrient supplementation, modification of food choices, and fortification. These interventions are effective, but not too sustainable in most rural communities in Ghana because of low funding. In Northern Ghana, such interventions have not reached a higher percentage of most malnourished people in rural communities. Indirect interventions address the underlying determinants of malnutrition, which include biofortification. Biofortification is a novel intervention in preventing micronutrient malnutrition. It involves the process of escalating the content and/or bioavailability of important nutrients in crops during plant maturation through genetic and agronomic pathways [16]. Genetic biofortification entails either genetic engineering or classical breeding whereas agronomic biofortification involves the proper application of micronutrient-rich fertilizer to the soil or unto the leaves through foliar means [17]. Biofortification targets starchy staple crops with low micronutrient content, such as rice, wheat, maize, sorghum, millet, sweet potato, and legumes. The reason for this is that they dominate diets around the world—particularly among the rural poor in developing and underdeveloped countries—and provide an affordable way to reach malnourished populations [17].

Biofortification has the potential of improving the nutritional content of the staple foods (maize, millet, rice, legumes) poor people in Northern Ghana consume, providing a comparatively inexpensive, cost-effective, sustainable, extended means of giving more micronutrients to the rural poor, especially in northern Ghana. This approach not only will lower the number of severely malnourished people who require treatment by complementary interventions, but also will help them maintain improved nutritional levels [16]. Biofortified crops are vital since they may serve as a nutritional buffer during economic shocks because the poor normally reduce their intake of higher-value food commodities when economic challenges occur [18]. Hence, the poor in Northern Ghana, who suffer from economic drought, are

Micronutrient	Rate of deficiency (%)
Ca	54
Zn	40
Se	28
I	19
Fe	5

Table 1.
Table indicating the rate of deficiency of essential micronutrients like Ca, Zn, Se, I, and Fe in Africa [4].

	Northern belt	Southern belt	Middle belt
Rate of anaemia (%)	53.2	28.2	32.3
IDA (%)	30	<8	<8

Table 2.
Table indicating the rate of anemia and IDA in the Northern, Middle, and Southern belts of Ghana [10].

	Stunting (%)	Overweight (%)	Wasting (%)
Upper east	36.1	18.4	11
Upper west	36.1	18.4	11
Northern	36.1	18.4	11

Table 3.
Table representing the rate of malnutrition among 0–59 months old children in the three Northern Regions of Ghana using stunting, overweight, and wasting as indicators [8, 9].

protected against severe micronutrient malnutrition. Biofortification moreover, gives a practical means of extending to malnourished rural populations in Northern Ghana, who may have limited access to commercially merchandised fortified foods and supplements. Most rural populations in Northern Ghana cannot afford to consume fortified foods and supplements, hence the need for the cultivation of biofortified crops. Compared to other micronutrient malnutrition interventions like food fortification, iron supplementation, among others, biofortification is highly cost-effective and very sustainable [19]. Nutritional targets for biofortification include elevated mineral content, improved vitamin content, increased essential amino acid levels, improved fatty acid composition, and increased antioxidant levels in crops [20].

Therefore, the primary goal of this systematic review is to discuss the three basic forms of biofortification, their significance, and how each type is capable of contributing to the prevention of micronutrient deficiency in the northern part of Ghana. This study will also suggest possible measures that need to be put in place to ensure the effective application of biofortification towards preventing micronutrient malnutrition in northern Ghana (**Tables 1–3**).

2. Types of biofortification

2.1 Biofortification through transgenic means

This strategy typically relies on simple access to a large genetic pool for the movement and expression of desired genes across two plant types that are not related to each other in terms of evolutionary or taxonomic standing [21]. When some micronutrients are lacking in crops, transgenic approaches is an effective way of fortifying the crop with those nutrients [22]. Transgenic approaches include genes that increase micronutrient concentration and bioavailability while decreasing anti-nutrient concentration, which reduces plant nutrient bioavailability.

Developing biofortified crops through the transgenic method requires a significant amount of time, effort, and investment during the research and development stage, but it is a cost-effective and sustainable approach in the long run, unlike nutrition-based organizational and agronomic biofortification programs [22–24]. Transgenic developed crops with enhanced micronutrient contents are capable of reducing micronutrient malnutrition among their consumers, most specifically, poor people in developing countries. In Northern Ghana, this method of biofortification has the potential to reduce micronutrient malnutrition.

Ever since the introduction of genetically modified (GM) crops in Ghana in 2013, there have been several debates regarding the health implications of these crops. Some advocacy groups in Ghana kicked against its introduction and they argue that GM food is not conducive to good health. Proponents also argue that GM crops, engineered to resist common pests, increase yield, and hence lead to rising incomes for farmers and the country in general.

In Northern Ghana, there is little knowledge about the advantages of GM seeds. Because of the counter debates on GM crops, most rural farmers have the perception that it is unhealthy for consumption. Some groups, such as The National Seed Trade Association of Ghana (NASTAG), are outspoken supporters of the use of GM seeds in Ghana. They hope it will boost agricultural development and help offset the consequences of climate change [25]. According to them, the incorporation of GM seeds in West Africa will help reduce the number of pesticides and time it takes for farmers to spray, which is proven scientifically to be true [26].

There is a need for more education and advocacy in Northern Ghana on the benefits of GM crops. Farmers should be given education about GM crops and their advantages. A couple of advances has been made in transgenic biofortification. The development of transgenic rice, maize, wheat, potatoes, beans among others have helped reduce the rate of micronutrient malnutrition in many underdeveloped communities. In northern Ghana, since most of their staple crops are maize, millet, beans, and potatoes, the use of transgenic maize, beans, millet, and potatoes rich in iron, vitamin a, zinc and other essential micronutrients will help in the fight against micronutrient malnutrition.

2.1.1 Transgenic maize

Maize is one of the most important staple crops grown in Northern Ghana. Just like other staple crops, maize contains very little amount of vitamin. However, provitamin A (carotenoid) is present in its endosperm due to the production of bacterial crtB [27] and several carotenogenic genes [28, 29]. Vitamin E and its synthetic analogs are powerful antioxidants with good effects on human health, and several research organizations are focusing biofortification of these constituents in maize. The iron content of maize has been increased by expressing soybean ferritin and Aspergillus phytase [29], soybean ferritin [30], Aspergillus Niger phyA2 [31], as well as inhibiting the expression of the ATP-binding cassette transporter and the multidrug resistance-associated protein [32]. A notable example is the BVLA4 30101 cultivar, which was released by Origin Agritech China and is biofortified transgenically for phytate decomposition. Maize's amino acid balance has been improved by the presence of milk protein-lactalbumin [33].

2.1.2 Transgenic common beans

One of the most important grain legumes used for human consumption is the common bean. In northern Ghana, it is one of the common crops grown by farmers. Most people consume it in its whole form. The expression of methionine-rich storage albumin from Brazil nut has helped to increase the methionine content of common bean [34].

2.1.3 Transgenic sweet potato

The nutritional properties of sweet potato have further been enhanced transgenically by increasing the contents of carotene, lutein, and total carotenoids by overexpressing the orange IbOr-Ins gene in white-fleshed sweet potato [35].

2.2 Biofortification through agronomic means

This method involves the physical application of nutrients to temporarily improve the nutritional and health status of crops and consuming such crops improves the human nutritional status [36]. This method is very common among farmers in Ghana. For instance, in the Northern part of Ghana, most peasant farmers buy fertilizers that contain macronutrients like nitrogen (N), phosphorus (P), and potassium (K) and apply them to staple crops like maize, to improve the crop yield and its nutritional composition. Macrominerals like nitrogen, phosphorus, and potassium (NPK) contribute a lot to the attainment of higher crop yields [37]. Through the application of NPK-containing fertilizers, agricultural productivity increased in many countries around the world in the late 1960s, resulting in Green Revolution, and saving them from starvation [38]. These fertilizers are vital in improving crop yield and are capable of saving the human population from starvation.

Agronomic biofortification is simple and inexpensive but needs special attention in terms of source of nutrients, application method, and effects on the environment [21]. It must therefore be applied frequently in every season to ensure maximum yield of the crops.

Some soil that promotes the development of microorganisms is utilized to raise the nutritional quality of plants by improving nutrient mobility from soil to edible sections. Some soil microbes, including Bacillus, Pseudomonas, Rhizobium, and Azotobacter species, are utilized to boost the phytoavailability of mineral elements [39, 40]. Some examples of crops that have been targeted through agronomical biofortification to improve the human nutritional status include the following:

2.2.1 Rice

Rice staples usually contain a low amount of micronutrients like iron and zinc. One way that can help incorporate such micronutrients into rice staples is through rice agronomic biofortification. Biofortification of rice plants by foliar spray of iron was an effective way to promote iron concentration in rice grains [41–43]. Similarly, the fortification of germinating rice plantlets with ferrous sulfate increases the iron concentration in germinated brown rice up to 15.6 times more than the original [42]. The foliar application of zinc is a successful agronomic approach that increases the concentration and bioavailability of zinc in rice grains [43–49]. The effective use of these agronomic rice biofortification techniques in northern Ghana has the potential to reduce micronutrient deficiency, particularly in rural areas.

2.2.2 Maize

The role of zinc in obtaining nutrient-enriched and high-yield grains like maize cannot be overemphasized. To achieve this, various zinc fertilizer treatments and foliar applications have been carried out in the maize crop [50–53]. These methods have proven to be an effective way of increasing the nutritional content of staple maize crops. The use of maize crops with increased zinc content will help reduce zinc deficiency in northern Ghana.

2.2.3 Common bean

Beans are a good vehicle for zinc biofortification and have been enriched with zinc by the application of foliar zinc fertilizer [49, 54]. This method is an effective way of enriching common beans with zinc, however, because of the cost; most farmers in northern Ghana are not able to afford it.

There is therefore the need for government to leverage the above innovations to support rural farmers in Northern Ghana and beyond. Controlled application of agronomic biofortification in Northern Ghana will increase the nutrient density and crop yield of common staple crops like maize, millet, beans, sorghum, and rice.

2.2.4 Sweet potato

An increase in beta-carotene in orange-fleshed sweet potato has been observed with irrigation and chemical fertilizer treatments [55]. This is also a very effective method of reducing micronutrient malnutrition in northern Ghana. Several studies have been conducted in Ghana about orange-fleshed sweet potato and its effectiveness in reducing vitamin A deficiency. Therefore, building on available evidence to advocate the consumption of orange-fleshed sweet potato in northern Ghana will help fight chronic vitamin A deficiency.

2.3 Biofortification through breeding

Compared to transgenic and agronomic strategies, biofortification through breeding is more cost-effective and sustainable [21]. In conventional plant breeding, parent lines with high nutrients are crossed with recipient lines with desirable agronomic traits over several generations to produce plants with desired nutrient and agronomic traits [21]. Several organizations are working hard to reduce micronutrient malnutrition using biofortification through breeding. For example, HarvestPlus is investing heavily to boost three key nutrients-vitamin A, iron, and zinc and is targeting the staple crops, wheat, rice, maize, cassava, pearl millet, beans, and sweet potato in Asia and Africa. They are carrying out several projects to produce staple food crops with improved levels of bioavailable essential minerals and vitamins that will have a measurable impact on improving the micronutrient level of target populations, primarily resource-poor people in the developing world, just like in northern Ghana. Because of better acceptability, several staple crops have been targeted for biofortification through crop breeding. They include the following:

2.3.1 Rice breeding

Milled rice has a poor source of minerals and essential micronutrients. Different old rice varieties with a high amount of iron and zinc content in grain have been screened and the higher mineral trait has been combined with improved agronomic traits by breeding methods [21]. In Asia, countries like India, Indonesia, and Bangladesh cultivate zinc rice varieties. Among the Caribbean, Nicaragua, El Salvador and Colombia also cultivate Rice variety. The government of Ghana must therefore invest in rice breeding to help in the fight against micronutrient malnutrition.

2.3.2 Millet breeding

The cheapest source of iron and zinc is pearl millet [56] and large variation has been seen in its germplasm for these micronutrients [57]. Iron pearl millet is currently being tested in Ghana. The development of this variety has the potential of reducing Iron deficiency in Northern Ghana.

2.3.3 Maize breeding

Maize is a cash crop grown for animal feed, industrial purposes (source of sugar, oil, starch, and ethanol), and use for human consumption [21]. Maize is genetically diverse, and for that matter, it has been a basis for the breeding programs that have helped generate highly nutritious maize crops. The majority of farmers in northern Ghana grow maize. Proper education on maize breeding to these farmers will help in the fight against

	Iron pearl millet	**Vitamin A cassava**	**Vitamin A maize**	**Vitamin A orange sweet potato**
Ghana	Under testing	Released	Released	Released

Table 4.
Table indicating a variety of Biofortified crops released or under testing in Ghana, developed through breeding [58].

Figure 1.
Biofortified rice. Source: Passion in Food and Field (Wordpress.com).

Figure 2.
Vitamin A Biofortified maize. Source: Crop Trust.

'hidden hunger' in northern Ghana. Furthermore, the Government must invest in maize breeding in northern Ghana to help prevent micronutrient deficiency (**Table 4**).

Examples of biofortified crops that are commonly consumed in Northern Ghana (**Figures 1** and **2**).

3. Methodology

3.1 Search strategy

A thorough search of available data on the topic was conducted using GOOGLE SCHOLAR. Other articles were obtained from PUBMED and ScienceDirect. The year limit was from 2007 to 2021. This was done to identify the latest publications on the topic. However, two articles published in 1999 and one paper from 2003 were included because of their level of relevance to the topic. A manual search was also conducted in the reference list of relevant literature related to the main research topic. The search terms used include, "Biofortification" and "Malnutrition", "Micronutrient Deficiency" and "Ghana", "Biofortification" and "Africa", "Micronutrient Malnutrition" and "Northern Ghana", "Biofortification" and "Types", "Northern Ghana" and "Malnutrition"

3.2 Inclusion and exclusion criteria

Papers were excluded if they did not fall within the year range, 2007–2021 except for two important articles published in 1999 and one paper from 2003. Only papers published in the English language were considered for review. Much priority was given to articles published in developing and underdeveloped countries since such countries record higher cases of malnutrition globally, of which Ghana is an example. In addition, the study focused on common staple foods available in Northern Ghana, which can easily be biofortified with essential micronutrients. Staples were excluded if they are not commonly cultivated in Northern Ghana. All study designs qualified for inclusion and there was no discrimination on gender.

4. Results

4.1 Search results

Hundred papers were obtained from the electronic search. A Thorough search for duplicates was conducted to ensure papers were not represented twice. Forty-one duplicates were removed, leaving 59 papers. Twenty-four papers were removed after screening all titles and abstracts. After a thorough screening, 35 papers for accepted for review. Some of the articles were thesis publications, others were review papers and the remaining were research papers.

4.2 Data extraction

- Publication details (author, date of publication),
- Country
- Population

• Language

• Results

4.3 Main findings

It was discovered from the reviewed articles that, the rate of micronutrient malnutrition is quite high, most especially in developing and underdeveloped countries. Major micronutrients like iron, zinc, iodine, and vitamin A are deficient in most diets worldwide. Biofortification was found to be an innovative technology that is capable of fighting micronutrient malnutrition in most developing and underdeveloped countries. All the studies recorded that, there are three major types of biofortification, which include, transgenic, breeding, and agronomic biofortification. About five studies from the review recorded that, micronutrient malnutrition was highest in Northern Ghana (Northern, Upper East, and Upper West regions), compared to other regions in Ghana. One study compared the three types of biofortification and discovered that biofortification through breeding is more cost-effective and sustainable compared to agronomic and transgenic biofortification. Other studies recorded that, several misconceptions exist about the consumption of crops developed through the transgenic method. They have a bad perception of its health implications. Finally, from the review, it was discovered that, few crop research centers exist to study all three types and how they can help prevent micronutrient malnutrition in Northern Ghana.

5. Conclusion and recommendations

All three major types of biofortification have a great potential in contributing to the fight against malnutrition in Northern Ghana as they are applicable in improving the nutritional quality of millet, rice, maize, sweet potato, and common beans which are staples common in the region. To achieve this, there is a need for more crop research centers to be set up in this region to develop more improved varieties that can help improve the nutritional status of the indigenous people in the region. Again, more education on the benefits of biofortified crops should be done in the region to encourage a shift towards the production and consumption of these nutrient-rich varieties. More research on the health benefits of transgenic biofortified crops is needed to ensure effective application of the method towards fighting micronutrient malnutrition in Northern Ghana. Current data on micronutrient malnutrition in Northern Ghana is needed to ensure the effective implementation of governmental policies.

Authors' contribution

ABK developed the research concept, formulated the research outline and carried out the systematic review of the paper. IA carefully reviewed the abstract, introduction and conclusion of the review. VA carefully scrutinized all aspects of the research to check for mistakes and make corrections to the paper.

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There was no conflict of interest recorded in this review.

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Chapter 6

Fight Hidden Hunger through National Programs and Food Based Approaches

Latika Yadav and Neelesh Kumar Maurya

Abstract

Nearly 2 billion people, or one-third of the world's population, suffer from micronutrient deficiencies. Micronutrient deficiencies or hidden hunger and the negative consequences of a diet deficient in essential vitamins, minerals, or trace elements continue to be serious public health concerns among Indians. This hidden hunger is especially prevalent among vulnerable populations, such as pregnant women, small children, and teenagers. As a result, the government has developed many national initiatives to combat malnutrition and micronutrient deficiencies, including ICDS, NFSM, Poshan Abhiyan, Swachh Bharat Abhiyan, and others. Governments also use food-based techniques to combat malnutrition and hidden hunger, including supplementation, food fortification, bio-fortification, and dietary diversification. This chapter presents statistics from the NFHS 4 and 5 and numerous national programs and food-based measures taken by governments to combat hidden hunger.

Keywords: hidden hunger, National Program, food fortification, micronutrients, food supplementation

1. Introduction

Hunger is a complicated issue, and several names are used to characterize its varied manifestations.

Generally, the term "hunger" refers to the distress caused by a deficiency of caloric. According to the United Nations' Hunger Report, hunger states "define periods when populations are facing significant food insecurity" in which people do not have enough food to survive. Hunger, according to the FAO, is defined as a circumstance in which a person has an unusual and uncomfortable feeling as a result of a deficiency of food components in their diet that is required for a healthy life.

Undernutrition is defined as a deficiency in calories or one or more important nutrients. Undernutrition can arise individuals are unable to get or prepare food, have a disorder that makes it difficult to eat or absorb food or require an excessive amount of calories. Undernutrition is frequently visible: people are underweight, their bones frequently fall out, their skin is dry and stretchy, and their hair is dry and starts falling out. Clinicians can usually diagnose malnutrition based on a person's appearance, height and weight, and overall health (including information about diet and weight loss). Food is provided to people through the mouth, if possible, in progressively increasing volumes, but it is also supplied via a tube carried from the throat to the stomach or put into a vein (intravenously). Undernutrition is commonly assumed to be caused by a lack of calories (i.e., overall food consumption) or protein. Vitamin and mineral deficiencies are so often thought to be different illnesses. However, when there is a calorie deficiency, vitamins and minerals are often more likely to be present. These, in turn, are the result of several factors, including household food insecurity, poor maternal health or childcare practices, and a lack of access to health services, safe drinking water, and sanitation.

Malnutrition refers to both under- and over-nutrition. Micronutrient deficiency occurs when vitamin and mineral intake or absorption is insufficient to sustain healthy growth and development in children and proper physical and mental function in adults. Poor nutrition, disease, or unmet micronutrient needs during pregnancy and lactation could all be contributing factors [1]. Over 2 billion individuals worldwide suffer from hidden hunger, more than double the 805 million people who do not get enough calories to consume [2]. The subcontinent of South Asia and much of Sub-Saharan Africa are hotspots for hidden hunger. In Latin America and the Caribbean, where diets are less reliant on single staples and where intensive micronutrient interventions, nutrition education, and basic health care are more prevalent, the rates are lower [3]. While the poorest countries bear a disproportionate amount of the expense of hidden hunger, micronutrient deficiencies, especially iron and iodine deficiency, are also widespread in the developed world. The worldwide malnutrition problem is becoming more complicated. Developing countries are shifting away from traditional diets based on minimally processed foods and toward highly processed, energy-dense, micronutrient-deficient foods, and beverages, which contribute to obesity and chronic diseases linked to diet. As a result of this nutritional change, many developing countries are experiencing the "triple burden" of malnutrition, micronutrient deficiencies, and obesity [4]. As a result, people's food does not provide the vitamins and minerals they require for proper growth and development. It has an impact on two billion individuals all over the world [5]. Micronutrient deficiencies are thought to be responsible for 1.1 million of the 3.1 million children who die each year due to malnutrition [6, 7]. By impairing the immune system, vitamin A and zinc deficiency have a negative impact on children's health and survival. Zinc deficiency inhibits growth in children and can cause stunting. Iodine and iron deficiencies hampered children's physical and intellectual development [8].

Women and children have higher dietary needs than men [9]. Throughout pregnancy and conception, the nutritional state of women has a long-term impact on the fetus's growth and development. Iodine deficiency causes nearly 18 million infants to be born with brain damage each year. Severe anemia is responsible for the deaths of 50,000 women each year after giving birth. In addition, 40 percent of women in impoverished countries suffer from an iron deficiency, which saps their energy. Women, infants, and young children are the primary targets of most initiatives to eliminate hidden hunger and improve nutrition outcomes. Treatments that focus on these people can have a high rate of return on investment by improving later-life health, nutrition, and cognition. Iodine, iron, zinc, and other micronutrient deficits are the most commonly identified micronutrient deficiencies in people of all ages (**Table 1**). Vitamin A deficiency affects an estimated 190 million preschool children and 19 million pregnant women [10], making it a less common but significant public health issue. Other important micronutrients, such as calcium, vitamin D, and B

Micronutrients deficiency	Effects
Vitamin A	Visual impairment, night blindness, increased risk of severe illness and death from common infections; (in pregnant women) night blindness, increased risk of death
Vitamin D	Mood changes, bone loss, muscle cramps, bone and joint pain, fatigue
Vitamin B12	Fatigue, breathlessness, numbness, poor balance and memory trouble.
Folic Acid	Megaloblastic anemia
Iron	Anemia, impaired motor and cognitive development, increased risk of maternal mortality, premature births, low birth weight, low energy
Iodine	Brain damage in newborns, reduced mental capacity, goiter
Zinc	Weakened immune system, more frequent infections, stunting

Table 1.
Micronutrient deficiencies and their effects on people.

vitamins like folate, are typically insufficient [11]. Although concealed hunger is most commonly associated with pregnant women, toddlers, and teenagers, it affects people at all stages of their lives. The major objective of this chapter is to present information regarding government programs and food-based techniques in industrialized countries like India to combat hidden hunger.

2. Methodology for the review of the literature

PubMed, Google, and other databases are searched for relevant material. We conducted a search of all review papers using the keywords "hidden hunger, malnutrition, India." Additionally, the global scenario, efforts, control programmes, critical evaluations, government reports, agency reports, and publicly available data were analyzed. The necessary data was gathered, compiled, and analyzed.

3. Rank of India in GHI

India's greatest national treasure is its children; nonetheless, hunger continues to be a significant threat to children's survival, growth, and development. It has assumed the proportions of a secret emergency in India. India is ranked 94th out of 107 analyzed countries on the 2020 Global Hunger Index (GHI), with a score of 27.2 for a "serious" level of hunger. Additionally, it states that wasting is "very prevalent" among children under the age of five in India. According to the Global Health Initiative, India has the greatest proportion of wasted children (children who are underweight for their height) of any country in the world (17.3 percent). Furthermore, India has 14% of malnourished children under the age of five and 34.7 percent of stunted children under the age of five. Whereas India ranks 101st out of 116 countries on the 2021 Global Hunger Index, with a score of 27.5, India has a severe level of hunger. Pakistan, Nepal, and Bangladesh, India's neighbors, have achieved a higher ranking. Nepal ranks 77th, Bangladesh ranks 76th, and Pakistan ranks 92nd [12, 13].

4. Outcomes of nutritional interventions

The National Family Health Surveys NFHS-4 (2015–2016) and NFHS-5 (2019–2021) data show falling patterns in some of India's important health characteristics as a result of these nutritional initiatives [14, 15].

4.1 Data on nutrition indicators as per the last available national survey (NFHS-5)

During the 2019–2020 academic year, the NFHS-5 collected data from around 6.1 lakh households. Many of the indicators in NFHS-5 are comparable to those in NFHS-4, which was conducted in 2015–2016 to allow for temporal comparisons. It serves as a tracking indicator for the country's Sustainable Development Goals (SDGs), which it wants to accomplish by 2030. Preschool education, disability, access to a toilet facility, death registration, bathing practices during menstruation, and techniques and reasons for abortion are all included in NFHS-5. New target areas in NFHS-5 will offer the necessary feedback for enhancing existing programs and developing new policy intervention techniques. Expanded domains of child immunization components of micronutrients for children are among the topics. Expanded age ranges for evaluating hypertension and diabetes among all people aged 15 and up are among the noncommunicable disease (NCD) components. The NFHS-5 asked for information on the percentage of women and men who had ever accessed the Internet for the first time in 2019.

4.2 Key findings of the NFHS-5

- 5% of children under the age of five are stunted (low height for their age).
- About 3% of children are wasted (low weight for height).
- 32% are underweight (low weight for their age).
- More crucially, according to the most recent national survey, 7.7% of children suffer from severe acute malnutrition.
- State-by-state, child nutrition indices indicate a heterogeneous pattern. While many states and UTs have seen improvements, some have seen a slight downturn.
- Malnutrition has gotten worse. Stunting has been raised in 11 out of 18 states. Wasting is going up in 14 states.
- Stunting: The percentage of stunted children has increased in 13 of the 22 states and UTs surveyed.
- Wasted: In comparison to NFHS-4, the percentage of children under the age of five wasted has increased in 12 of the 22 states and UTs surveyed.
- Obesity: The percentage of overweight children under the age of five has increased in 20 states and territories.

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- Children who had diarrhea in the 2 weeks prior to the study increased from 6.6 to 7.2 percent.

4.3 Related indicators

- Children under 6 months who were exclusively breastfed also showed a sharp improvement, going from 54.9 to 63.7%.
- The proportion of children (12–23 months) who were fully vaccinated improved from 62–76%.
- The proportion of anemic children (5–59 months) increased from 58–67%.
- Women aged 15–49 who were anemic increased from 53–57% and men of the same age increased from 29–31% between both editions of the NFHS.
- In most states and UTs, the sex ratio at birth (SRB) has remained constant or increased.
- The majority of the states are at a normal sex ratio of 952 or above.
- SRB is below 900 in Telangana, Himachal Pradesh, Goa, Dadra & Nagar Haveli, and Daman & Diu.
- States such as Tripura, Manipur, Andhra Pradesh, Himachal Pradesh, and Nagaland have also shown an increase in teenage pregnancies.
- Children in the age group (6–23 months) receiving an adequate diet also showed a sharp improvement, from 9.6 to 11.3%.

4.4 The status of child mortality in India

- Between 2019 and 2021, the U5MR dropped dramatically from 49.7 to 41.9%.
- In India, the U5MR is 41.9 per 1000 live births, whereas the IMR is 35.2/1000 live births, and the NMR is 24.9 per 1000 live births.
- Infant and child mortality rates have decreased in most Indian states. The best performers were Sikkim, Jammu & Kashmir, Goa, and Assam, which saw significant reductions in neonatal mortality rate (NMR), infant mortality rate (IMR), and under-five mortality rate (U5MR).
- All three categories of child mortality increased in Tripura, Andaman & Nicobar Island, Meghalaya, and Manipur.
- Among the 22 states and union territories surveyed, Bihar had the highest prevalence of NMR (34), IMR (47), and U5MR (56), whereas Kerala had the lowest death rates.
- In the last 5 years, Maharashtra's child mortality rate has remained unchanged.

- Improved Sanitation and Cooking Facilities: Over the last 4 years, the percentage of households with improved sanitation and clean cooking fuel has increased in almost all of the 22 states and UTs (from 2015 to 2016 to 2019–2020).

- Anemia among women and children continues to be a cause of concern. In 13 of the 22 states and UTs, more than half of the children and women are anemic. In addition, despite a significant increase in the consumption of IFA tablets by pregnant women for 180 days or more, anemia among pregnant women has increased in half of the States/UTs compared to NFHS-4.

The state of hidden hunger in India is alarming. A lot of work has been done, and while progress has been made, the pace of improvement is too slow.

5. An initiative taken by the Indian government to tackle hidden hunger

5.1 Direct policy measures

5.1.1 Integrated child development services (ICDS)

Integrated Child Development Services (ICDS) is an Indian government programme that provides Supplementary nutrition, nutrition and health education, vaccinations, health screenings, referral services to children and their mothers under the age of six, non-formal pre-school education, and contraceptive counseling for teenagers. The scheme was initiated in 1975, suspended in 1978 under Morarji Desai's government, and then reintroduced under the Tenth Five Year Plan. The tenth five-year plan also established a link between ICDS and Anganwadi centers, which are primarily located in rural regions and manned by frontline workers. Along with boosting child nutrition and immunization, the initiative aims to eliminate gender inequality by ensuring equitable access to resources for girls and boys [16].

5.1.2 Mid-day meal scheme

The Midday Meal Scheme is a school meal program in India that aims to improve the nutritional status of school-aged children across the country. On working days, the program provides free lunch to children in primary and upper primary classes who attend government, government-aided, local body, Education Guarantee Scheme, and alternative innovative education centers, Madarsa and Maqtabs, supported by the Sarva Shiksha Abhiyan, and Ministry of Labour-run National Child Labour Project schools. With 120 million children served in 1.27 million schools and Education Guarantee Scheme centers, the Midday Meal Scheme is the world's largest of its kind. In September 2021, the MoE (Ministry of Education), which serves as the scheme's nodal ministry, changed the scheme's name to PM-POSHAN (Pradhan Mantri Poshan Shakti Nirman) Scheme. According to the Central Government, by 2022, the scheme would cover an extra 24 lakh children getting pre-primary education at government and government-aided institutions. The program has undergone various adjustments since its introduction in 1995. The Midday Meal Scheme is established by the National Food Security Act of 2013. The National School Lunch Act in the United States is the legal basis for the Indian school lunch program.

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5.1.3 National Health Mission

The National Health Mission (NHM), which combines the National Rural Health Mission with the National Urban Health Mission, was announced by the Indian government in 2013. It was renewed in March 2018 for another year, till March 2020. It is headed by a Mission Director and controlled by National Level Monitors chosen by the Government of India. The National Health Mission (NHM) is responsible for several key initiatives, including Rogi Kalyan Samiti, Hospital Management Society, Untied Grants to Sub-Centres, Health Care Contractors, Accredited Social Health Activists National Mobile Medical Units (NMMUs), Janani Suraksha Yojana, National Ambulance Services Some of the initiatives include Janani Shishu Suraksha Karyakram (JSSK), Rashtriya Bal Swasthya Karyakram (RBSK), maternal and child health wings (MCH Wings), free medications and diagnostic services, district hospital and knowledge center (DHKC), National Iron+ Initiative, and tribal tuberculosis eradication.

5.1.4 Rajiv Gandhi schemes for the empowerment of adolescent girls (RGSEAG)

SABLA is another name for this program. The initiative was unveiled by the Indian government on November 19, 2010, in the Plenary Hall of the Vigyan Bhavan in New Delhi. According to the Plan, adolescent girls between the ages of 11 and 18 will be included in all ICDS programs. The scheme's goals are to help adolescent girls achieve self-development and empowerment, improve their nutrition and health, raise awareness about health, hygiene, nutrition, adolescent reproductive and sexual health (ARSH), and family and child care, improve their home-based skills, life skills, and vocational skills, mainstream out-of-school adolescent girls into formal or non-formal education, and inform and guide adolescent girls.

5.1.5 Indira Gandhi Matritva Sahyog Yojna (IGMSY) (a conditional maternity benefit scheme)

Under IGMSY a centrally sponsored scheme sanctioned by the Government of India in October 2010 under which grant-in-aid is distributed to states and UTs. promoting (ideal) infant and young child feeding (IYCF) practices, particularly early and exclusive breastfeeding for the first 6 months; and contributing to a more supportive environment by providing economic incentives to pregnant and nursing mothers for improved health and nutrition.

5.1.6 Mission for integrated development of horticulture schemes

The National Horticulture Mission (NHM) is one of the sub-schemes of the Mission for Integrated Development of Horticulture (MIDH), and it is implemented through State Horticulture Missions (SHM) in selected districts across 18 states and six union territories. Farmers or beneficiaries should contact the district's Horticulture Officer to receive benefits and assistance under the scheme.

5.1.7 National Food Security Mission

The government of India introduced this centrally funded initiative, termed the "National Food Security Mission," in October 2007 in response to stagnated foodgrain output and an increasing consumption requirement of India's growing population.

The mission was a spectacular success, with increased output of rice, wheat, and pulses. During the 12th Five Year Plan, the mission was expanded with new targets of an additional 25 million tonnes of food grain output by the end of the Plan, including 10 million tonnes of rice, 8 million tonnes of wheat, 4 million tonnes of pulses, and 3 million tonnes of coarse cereals. Based on previous experience and the performance of the 12th Plan, the program has been extended to 2019–2020, corresponding with the Fourteenth Finance Commission (FFC) period. Rice will account for 5 million tonnes, wheat will account for 3 million tonnes, pulses will account for 3 million tonnes, and coarse cereals will account for 2 million tonnes, to increase foodgrain production by 13 million tonnes.

5.1.8 The mahatma Gandhi National Rural Employment Guarantee Scheme (MGNEREGS)

The Mahatma Gandhi Employment Guarantee Act 2005 (or, NREGA, later renamed as the "Mahatma Gandhi National Rural Employment Guarantee Act" or MGNREGA), is an Indian labour law and social security measure that aims to ensure the "right to work". This act was enacted on August 23, 2005 by Prime Minister Dr. Manmohan Singh's UPA government. It aims to improve rural residents' livelihood security by offering at least 100 days of paid employment per year to each household whose adult members volunteer to perform unskilled manual labour. The MGNREGA was established with the goal of "improving livelihood stability in rural regions by providing at least 100 days of guaranteed wage employment every fiscal year to every household with adult members who volunteer to perform unskilled manual work."

5.1.9 Swachh Bharat Abhiyan

The Swatchh Bharat Mission (SBM), also known as the Swatchh Bharat Abhiyan or the Clean India Mission, is an Indian government-led campaign to eliminate open defecation and improve solid waste management in 2014. It is a revamped version of the Nirmal Bharat Abhiyan, launched in 2009 but failed to achieve its goals. On October 2, 2014, Prime Minister Narendra Modi launched the campaign in Rajghat in New Delhi. With 3 million government workers and students from around the country participating in 4043 cities, towns, and rural villages, India's largest cleaning campaign to date.

5.1.10 The National Rural Drinking Water Program

On August 7, 2018, India's Comptroller and Auditor General (CAG) issued its findings on the "National Rural Drinking Water Programme." In 2009, the National Rural Drinking Water Program (NRDWP) was created. It strives to provide rural residents with safe and sufficient water for drinking, cooking, and other home requirements on a sustainable basis.

5.1.11 Eat right India campaign

On July 10th, 2018, FSSAI launched "The Eat Right Movement" to boost public health in India and counteract unfavorable nutritional trends associated with lifestyle disorders. On a unified platform, the food industry, public health specialists, civil society and consumer organizations, influencers and celebrities promised to make real efforts to magnify "The Eat Right Movement" in the country.

5.1.12 Poshan Abhiyan

On behalf of the Ministry of Women and Child Development, Prime Minister Narendra Modi launched the POSHAN Abhiyaan in Jhunjhunu, Rajasthan, in March 2018. Its goal is to reduce undernutrition and other related issues by organizing various nutrition-related programs. Stunting, malnutrition, anemia (especially among young children, women, and adolescent girls), and low birth rates are also addressed. It will oversee and evaluate the implementation of all such plans, using existing organizational structures within line ministries where possible. By 2022, it plans to expand interventions supported by the ongoing World Bank-funded ICDS Systems Strengthening and Nutrition Improvement Project (ISSNIP) to all districts in the country.

5.1.13 Pradhan Mantri Matru Vandana Yojana

The Ministry of Women and Child Development administers the Maternity Benefit Scheme, a federally funded program. It is a maternity benefit program that began on January 1, 2017, in all districts of the country.

5.1.14 National Food Security act

The National Food Security Act of 2013 (also known as the "Right to Food Act") is an Indian law that aims to provide subsidized food grains to about two-thirds of the country's 1.2 billion people. It was signed into law on September 12, 2013, with a retroactive date of July 5, 2013. The existing government of India's food security programs is converted into legal entitlements under the National Food Security Act, 2013 (NFSA 2013). The Midday Meal Program, Integrated Child Development Services Program, and Public Distribution System are all part of it. Furthermore, the NFSA 2013 recognizes maternity benefits. The Integrated Child Development Services Scheme and the Midday Meal Scheme are universal. In contrast, the PDS will serve roughly two-thirds of the population (75 percent in rural areas and 50 percent in urban areas).

5.1.15 Mission Indradhanush

The government of India's health mission is known as Indradhanush. Union Health Minister J. P. Nadda introduced it on December 25, 2014. The effort's goal is to achieve and maintain 90 percent vaccination coverage in India by 2020. Vaccination is available nationwide against eight vaccine-preventable diseases, including Diphtheria, Whooping Cough, Tetanus, Polio, Measles, a severe form of childhood tuberculosis, Hepatitis B, and meningitis and pneumonia caused by Haemophilus influenza type B, as well as Rotavirus diarrhea and Japanese Encephalitis in selected states and districts.

5.2 Indirect policy measures

- Increasing food grain production to ensure food security.
- By supporting the production and availability of nutritionally dense food items, we may endeavor to improve the population's dietary pattern.

- Increasing the poor's purchasing power and lowering their susceptibility in order for them to purchase a balanced, nutrition-dense diet.
- Expansion and improvement of the public distribution system
- Increasing student awareness of nutrition through school curricula, etc.
- Food adulteration should be monitored and prevented.
- Initiate more community involvement in nutrition surveillance.

6. Eradicating micronutrient deficiencies: Approaches based on food

The term "hidden hunger" refers to a more subtle sort of shortage produced by consuming inexpensive, satisfying foods that are low in important vitamins and minerals. While the implications of subclinical micronutrient deficiencies are becoming more understood and monitored, they frequently go unreported in the population. This is why vitamin deficits have been dubbed "hidden hunger." Micronutrient deficits can occur even in places with an adequate food supply to support the population's energy needs. When people cannot afford to diversify their diets sufficiently with fruits, vegetables, or animal-source foods containing micronutrients, shortages are unavoidable. Micronutrients are vitamins and minerals that humans require in order to boost cellular growth and metabolism. Iron, iodine, and vitamin A deficiency are the most prevalent forms of micronutrient malnutrition with serious public health effects. Other micronutrients have been demonstrated to contribute to illness prevention (e.g., folic acid and calcium) or growth promotion (e.g., zinc) [17].

FAO views food-based initiatives as a sustainable way to address the nutritional needs of population groupings. These are as follows:

1. Supplementation
2. Fortification
3. Bio-fortification
4. Dietary diversification
5. Community-based interventions for micronutrient status improvement

6.1 Supplementation

Supplementation is a technical term that refers to the process of delivering nutrients directly to the target population via syrup or pill. It has the advantage of providing an appropriate amount of a specific nutrient or nutrients in an easily absorbed form and is frequently the quickest option to address deficiency in people or demographic groups diagnosed as insufficient. Supplementation programmes are typically used as a temporary treatment and then phased out in favor of long-term, sustainable food-based interventions like fortification and dietary change, which typically involve increasing food diversity.

6.2 Fortification

By 2024, all rice available at ration shops, rice available in mid-day meals, and rice available through all schemes will be fortified, Prime Minister Narendra Modi declared during his 75th Independence Day address from the Red Fort in New Delhi. The Prime Minister's declaration is crucial for the nation and represents a forward-thinking strategy, as the government distributes approximately 300,000 tonnes of rice annually through various programmes authorized by the National Food Security Act, 2013. (NFSA). The Centre has allocated 328 lakh tonnes of rice under the NFSA for TPDS (Targeted Public Distribution System), MDM (Mid-day Meal), and ICDS (Integrated Child Development Services). Rice fortification will assist in addressing micronutrient deficiencies or "hidden hunger," both of which contribute to undernutrition, a type of malnutrition. But before we discuss the benefits of the aforementioned declaration, if done properly, let us first define fortification and why it is necessary to combat malnutrition in India [18]. Food fortification is a cost-effective, scalable, and sustainable worldwide solution that tackles micronutrient deficiency. In October 2016, the Food Safety and Standards Authority of India (FSSAI) operationalized the Food Safety and Standards (Fortification of Foods) Regulations, 2016 to fortify staple foods such as wheat flour and rice (with iron, vitamin B12, and folic acid), milk and edible oil (with vitamins A and D), and double fortified salt (with iodine and iron) in order to address India's high burden of micronutrient malnutrition. The "+F" symbol has been designated for the purpose of identifying fortified foods. Each package of fortified food shall bear the words "fortified with (fortificant name)" and the +F logo. Additionally, it may have the tagline "Sampoorna Poshan Swasth Jeevan" beneath the emblem, which is optional and not required (**Figure 1**) [19].

Fortification is the process of supplementing staple foods such as rice, wheat, oil, milk, and salt with essential vitamins and minerals such as iron, iodine, zinc, and vitamins A and D to increase their nutritional content. These nutrients may have been present in the food at the time of manufacture or may have been lost during processing.

6.2.1 Need of food fortification

Micronutrient deficiency or malnutrition, commonly referred to as "hidden hunger," is a severe health concern. Access to safe and nutritious food is critical, and

Figure 1.
Food fortification logo used on fortified foods in India in Hindi and English language. [Source: https://fssai.gov.in/knowledge-hub-logos.php?pages=2].

occasionally, owing to a lack of a balanced diet, a lack of variety in the diet, or food insecurity, individuals do not receive essential micronutrients. Often, significant minerals are lost during food processing as well. One strategy for addressing this issue is the fortification of food. This strategy complements other strategies for improving nutrition, such as diet variety and food supplementation. India suffers from a high rate of micronutrient deficiencies caused by Vitamin A, Iodine, Iron, and Folic Acid, which result in night blindness, goiter, anemia, and a variety of birth abnormalities. According to the National Family Health Survey (NFHS-4), anemia affects 58.4% of children aged 6 to 59 months, 53.1 percent of women of reproductive age, and 35.7 percent of children under the age of five. Fortification is an internationally proven technique that addresses the population's widespread vitamin deficiencies.

6.2.2 Benefits of food fortification

The benefit-to-cost ratio of food fortification is extremely favorable. According to the Copenhagen Consensus, every rupee spent on fortification results in an economic value of nine rupees. Although the equipment and vitamin and mineral premix require an initial investment, the ultimate cost of fortification is quite inexpensive. Even if all programme costs are passed on to customers, the price rise will be between 1 and 2 percent, which is less than the regular price variance. The following are some of the numerous advantages of food fortification:

- Because staple foods are extensively consumed, nutrients are added to them. Thus, this is an ideal way to simultaneously improve the health of a wide segment of the population.

- It is a safe approach to enhancing people's nutrition. The addition of micronutrients to food poses no risk to human health. The amount supplied is minimal and considerably below the Recommended Daily Allowances (RDA), and is strictly monitored to ensure safe use.

- It is a cost-effective strategy that does not require individuals to alter their dietary habits or eating patterns. It is a socially and culturally acceptable method of nutrient delivery.

- It has no effect on the food's properties such as taste, aroma, or texture [20].

In this circumstance, fortification is the most practical option in terms of population access. This is referred to as the fortification of staple foods. The government of India has recognized this truth. This is why standards for five fortified essentials have been released, along with a logo (+F) to distinguish fortified foods: wheat flour, rice, edible oil, milk, and Double Fortified Salt. Recently, regulations for processed meals such as breakfast cereals, buns, rusks, pasta, and noodles were also released. Additionally, in collaboration with Tata Trusts, the Food Fortification Resource Centre (FFRC) has been located at FSSAI under the Ministry of Health and Family Welfare. The Food Fortification Resource Centre (FFRC) is a non-profit organization dedicated to the advancement of food fortification. The FFRC was established as a resource hub to serve as a shared platform for bringing together all major actors in food, nutrition, and health to collaborate on eradicating hidden hunger (**Figure 2**) [21].

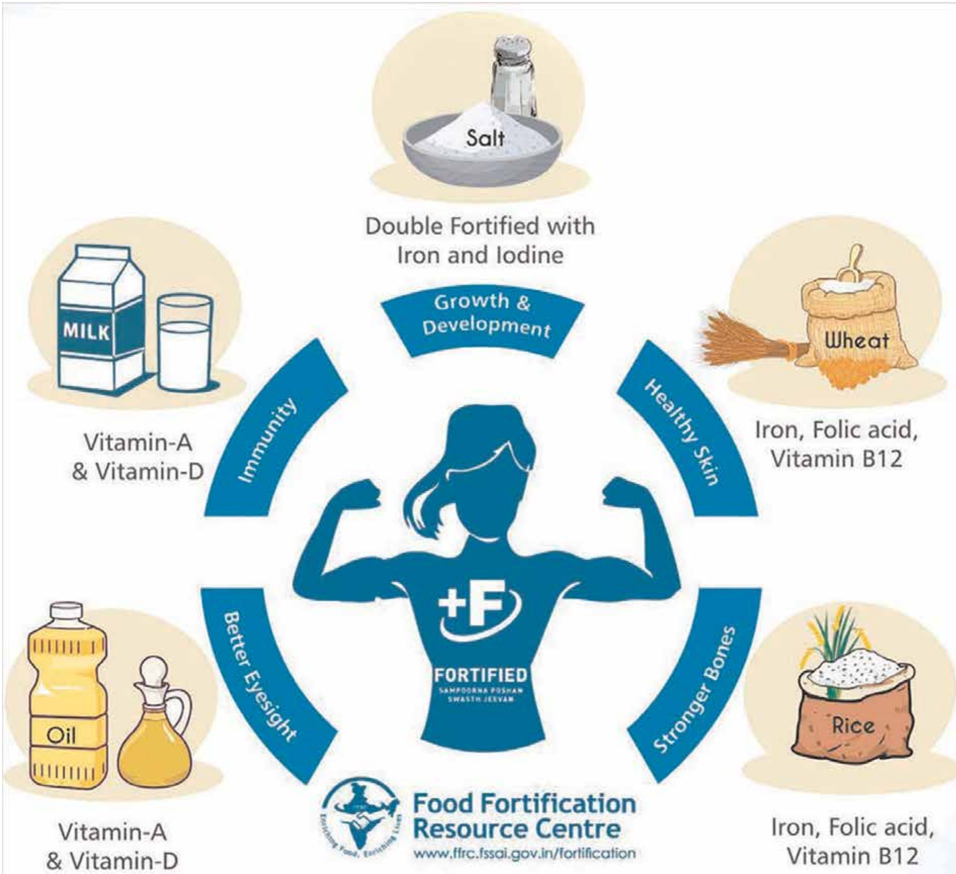

Figure 2.
Diagrammatic representation of food fortified with minerals and vitamins in India. [Source: https://www.insightsonindia.com/wp-content/uploads/2021/08/F.jpg].

6.2.3 Fortified foods

Salt is an excellent medium for iodine fortification and has been effectively used to combat iodine deficiency around the world. The properties of iodine salts used in fortification Salts of iodates and iodides in sodium and potassium are the two chemical forms employed in salt iodization. Fortification levels range between 30 and 200 parts per million. The WHO recommends that, under typical situations where salt is lost at a rate of 20% from manufacturing to household, an additional 20% be lost during cooking prior to consumption. The average person consumes 10 g of salt each day. This method was developed by the National Institute of Nutrition in Hyderabad to address the dual problems of iron and iodine deficiency. Given the widespread consumption of staple cereals, fortification makes sense. Wheat flour is enriched with iron and other minerals in various countries. There have been concerns concerning the bioavailability of iron from wheat atta due to its high phytate (absorption inhibitor) concentration. Certain chemicals, such as Na-Fe-EDTA and perhaps the enzyme phytase, may overcome phytate's inhibitory effect. The higher expense of this salt may be offset by the fact that it has a higher bioavailability and therefore requires less fortification. Rice is the staple food for more than half of India's population. Fortification of rice has been attempted by combining fortified extruded grains from rice flour with unfortified rice (Ultra rice). Wheat flour fortification with thiamin, riboflavin, niacin, and iron has been used successfully for a long period of time.

Vitamin A added to wheat flour showed excellent stability in studies conducted in the United States. In the Philippines and Sri Lanka, efficacy trials on wheat flour fortified with vitamin A and wheat flour fortified with iron are presently underway. Since late 1997, the United States and Canada have required wheat to be fortified with folic acid. In South America, in Chile and Costa Rica, fortification of wheat flour with folic acid has proved helpful in minimizing neural tube abnormalities. Zinc sulphate fortification of wheat flour was observed to decrease iron absorption; however, zinc oxide had no such inhibitory impact. Around 2.2 million tonnes of wheat flour are fortified in India. Since 2000, a few states, including Madhya Pradesh and Gujarat, and a few districts in West Bengal have fortified wheat flour. Numerous countries have enriched cereal products with folic acid to help minimize the prevalence of neural tube abnormalities. Fortification with folic acid, maybe in conjunction with vitamin B12, may also help reduce serum homocysteine levels. Because vitamin A is fat soluble, fats and oils may be useful carriers for it. In India and Pakistan, vegetable ghee (hydrogenated vegetable oil) is fortified. Margarine is vitamin A-fortified in approximately 24 countries, including Brazil, Chile, Colombia, Mexico, and Indonesia. Brazil is conducting trials on vitamin A-fortified soybean oil. Edible oils enriched with vitamin A and D are sold through market channels in India's Madhya Pradesh and Rajasthan regions. In Venezuela, vitamin A, thiamin, riboflavin, niacin, and iron are added to precooked corn flour. In countries such as Mexico, where corn is the predominant food, fortification of maize with micronutrients is being studied. Maize flour is fortified with iron, zinc, and a vitamin B complex. Maize flour was enriched with soy protein and examined for its ability to aid in the development of the brain in rats. Additionally, research is being conducted to strengthen corn tortillas on a home and industrial scale [22].

6.3 Biofortification

Biofortification is a method that increases the nutrient density of food crops through conventional plant breeding, enhanced agronomic practises, and/or current biotechnology without sacrificing any consumer or farmer-preferred trait [23]. It is acknowledged as a nutrition-sensitive agriculture strategy that has the potential to significantly minimize vitamin and mineral deficiencies [24–26]. Zinc biofortification of beans, cowpeas, and pearl millet, as well as provitamin A carotenoid biofortification of cassava, maize, rice, and sweet potato, are all ongoing and at various stages of development. The biological process by which biofortified crops improve nutritional status is straightforward: biofortified crops are more nutrient-dense than conventional crops. Individuals will consume [27] and absorb [28] more micronutrients by eating biofortified crops than by eating the same amount of non-biofortified crops, assuming comparable micronutrient bioavailability [29] and retention [30] following heating or processing and storage. Consumption of biofortified staple crops can increase micronutrient intake in communities with a diet deficient in these nutrients.

6.4 Dietary diversification

Increasing dietary diversity is one of the most effective strategies for preventing hidden hunger on a long-term basis [31]. Even when socioeconomic factors are controlled for, dietary diversity is related to improved child nutritional outcomes [32]. In the long run, dietary diversification promotes a balanced and appropriate intake of macronutrients (carbohydrates, lipids, and protein); necessary micronutrients; and additional food-derived compounds such as dietary fiber. The majority of people may receive adequate nutrition from a mix of cereals, legumes, fruits, vegetables, and animal-source foods. Certain populations, such as pregnant women, may require supplements [33]. Effective solutions for promoting dietary diversity include food-based tactics such as home gardening and educating people about proper infant and young child feeding practises, food preparation, and nutrient-saving storage and preservation methods. Several low-cost, food-based approaches for improving micronutrient status can be advocated at the community level. Culturally relevant dietary adjustments should be established to assist individuals in identifying concrete measures that can increase both food supply and micronutrient absorption. This information must be distributed to the public using conventional methods of communication.

6.5 Community-based interventions for micronutrient status improvement

- Promoting exclusive breastfeeding for newborns up to 6 months of age and continuing breastfeeding for older infants
- Identifying and promoting the use of culturally suitable micronutrient-dense weaning foods.
- Identifying and promoting the use of traditional green-leafed vegetables and fruits to increase dietary diversity.
- Micronutrient preservation in fruits and vegetables by solar drying or canning processes.
- Promoting kitchen gardening and small animal husbandry.
- Increasing year-round access to micronutrient-dense foods.

Numerous issues confront developing nations, including health care, education, sanitation, water supply, and housing. As a result, focusing exclusively on a specific vitamin shortfall or technique will not be the most effective way to reduce micronutrient deficiencies. Complementary public health measures that can help minimize micronutrient deficiency include deworming, malaria prevention, increased access to safe drinking water and sanitation, and childhood immunization. Successful plans address all of these issues holistically and cooperatively, with full political commitment.

7. Conclusions

India ranks 102 out of 116 countries in the Global Hunger Index 2021. While eliminating malnutrition in India would be tough, it is not impossible. Achieving a sustainable end to hunger needs prompt action. Over 2 billion people, or one-third of the world's population, are malnourished. Malnutrition and micronutrient deficiencies have a significant impact on child and mother mortality, mental impairment, and workforce productivity. The current paradigm of seeing food security only through the lens of energy security must change. Simply pumping grains to satisfy hunger will not provide nutrition and health. The objective should be to ensure that the diet is balanced in terms of macro-and micronutrients. To maintain MN security, laboratory, clinical, and community-based (operations) studies are required. A balanced approach of food fortification, dietary diversity, biofortification, and supplementation aided in the early detection and treatment of clinical deficiencies. A fortification program's performance can be judged in terms of its public health effects and sustainability. The mechanism for extension must be robust. Support from the media is critical for raising awareness and promoting compliance. Large-scale initiatives including food fortification, dietary diversity, biofortification, and micronutrient supplementation are making significant headway in lowering the morbidity and mortality associated with micronutrient deficiencies. Current programs must be enhanced and work on their effective implementation must be done to ensure that they reach the poor. While targeted legislation must be enacted to rein in the proliferation of schemes, the judiciary must be an active player in the debate on nutritional justice for the people.

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Conflict of interest

Authors declare no conflict of interest.

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Chapter 7

Malnutrition's Prevalence and Associated Factors

Arslan Ahmad, Sakhawat Riaz, Nosheen Ijaz, Maleeha Fatima and Muntaha Latif

Abstract

Malnutrition, which affects roughly 2 billion people worldwide, is among the country's most pressing health issues. In comparison to other developing nations, Pakistan has one of the worst prevalence of childhood malnutrition. We'll explore how people in poor countries manage food scarcity. Owing to low per capita income and a lack of purchasing power for fundamental food staples that meet the human body's nutritional demands. Malnourished children in Pakistan suffer from stunting, wasting, and being underweight. The causes of child malnutrition and stunting in Pakistan are discussed in this chapter, as well as the impact of numerous factors on stunting and the types of intervention methods and practices that should be devised and executed to address the problem.

Keywords: malnutrition, stunting, food insecurity, interventions, strategies

1. Introduction

Malnutrition is commonly referred to as under-nutrition [1]. Stunting, wasting, and being underweight in children under the age of five are all signs of malnutrition [2]. Malnutrition refers to any shortage, surplus, or volatility in energy and/or nutritional demands, and includes both under and over-nutrition [3, 4]. 165 million children under the age of five suffer from malnutrition across the world. India (46.6 million), Nigeria (13.9 million), and Pakistan (10.7 million) have the world's least stunted children, according to the 2018 Global Nutrition Report [5]. Malnutrition is responsible for at least half of all child deaths globally [6, 7]. Children's malnutrition is mostly a problem in developing and disadvantaged countries [8]. The leading cause of sickness and death among children is malnutrition [9]. Malnutrition is among the world's most serious health problems, affecting around 2 billion people. Malnutrition in all forms (appetite, undernourishment, vitamin deficiencies, overweight, and obesity) appears to be a severe concern for both emerging and industrialized countries, according to the World Committee on Food Security. Hunger may be characterized in many different ways, including individual experiences and behavioral reactions in the home, food shortages, and national food balance sheets [10]. Approximately 151 million children under the age of five are stunted, over 50 million are wasted, and nearly

17 million are seriously wasted, according to UNICEF/WHO/World Bank Group estimates [11, 12]. Although the total rate of stunting in Asia has decreased from 38 percent to 23 percent between 2000 and 2017, it is still the highest [13].

Pakistan is now experiencing a complicated malnutrition problem that affects people of all ages, especially newborns, children, adolescents, and pregnant and nursing mothers. As per UN Worldometer statistics, Pakistan's population is now predicted to be about 219.1 million, with a potential increase to >260 million by 2030 [14]. Malnutrition is predicted to cost emerging nations between 2 and 3% of their GDP (GDP). Malnutrition is estimated to cost a person one-tenth of their lifetime wages [15]. Pakistan has a high rate of malnutrition. As a result, nearly a quarter of the population of a low-middle-income, fifth nation is unable to meet an adult's dietary needs (2350 calories per day) [16–18]. According to a recent global report on child malnutrition, The majority of households in low and middle-income countries are facing dual-faced malnutrition as a result of a dietary shift, which is defined as a home with an obese mother and an undernourished child. On the other hand, stunting is declining relatively slow, whereas excess weight continues to rise globally [19]. As a result, while establishing policies, programs, and interventions to prevent undernutrition, food insecurity and dietary variety should be considered [20].

2. Childhood stunting's causes

Stunting develops in children as a result of a regular caloric intake and nutrients that are insufficient to meet their needs. A lack of linear development, or a modest stature or height in one's age, is referred to as stunting. This is evaluated by dividing a child's height for his or her age to either a comparison group of well-fed and healthy children (Z score of 2 or less). Stunting refers to excess or inequality in a person's energy or calorie consumption that is linked to stunted physical and psychological development [21]. Stunting is associated with the phrase "small for gestational age" (SGA) globally [22]. If pregnant women's nutritional demands are not addressed sufficiently, they might not be able to provide the fetus with the nourishment it needs during pregnancy. Malnourishment in pregnancy is a big issue in Pakistan since it can inhibit a baby's development and raise the risk of certain diseases later in life [23]. According to the United Nations Children's Fund, almost 10 million Pakistani children are stunted (UNICEF). For the first 6 months of their lives, just 38% of newborns are exclusively breastfed. As a result, more than half of children under the age of five are deficient in vitamin A, 40% are zinc and vitamin D deficient, and 62% are anemic. In Pakistan, 4 out of every 10 children under the age of five are stunted, with 40.2 percent wasting and 17.7% stunting. According to the 2018 national nutritional survey, more than one-third of children (28.9%) are underweight, with a high prevalence of overweight (9.5%) in the same age range shown in **Figure 1**.

The nutritional challenges of their children are linked to the moms' diet and wellness during adolescence, gestation, and breastfeeding periods. As a result, expectant moms must receive appropriate and balanced nourishment. Maternal micronutrient supplementation (MMS) during pregnancy improved gestation, birth weight, and fetal development in Tanzanian infants, as evidenced by their 6-week mortality rate, which was only quantifiable in females but not males newborns [24]. Due to compromised immune systems, malnutrition and infection combined to raise the risk of childhood morbidity and death. More than half of all children under the age of five are expected to die from malnutrition. Immunological changes have been associated with decreased intestinal activities, the

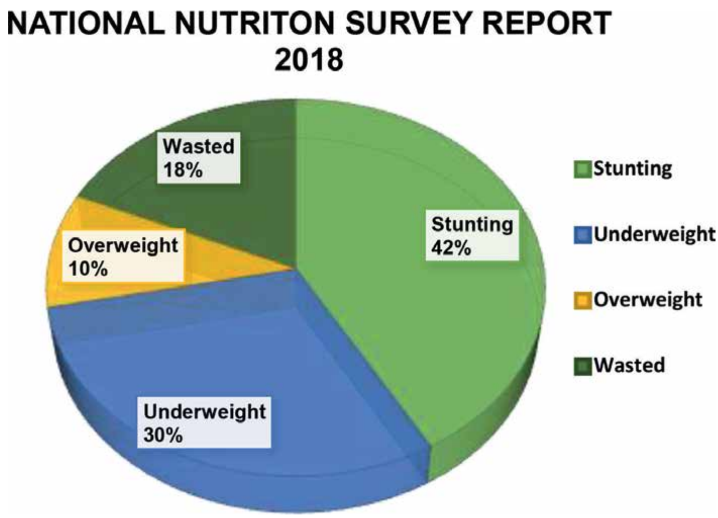

Figure 1.
National nutrition survey malnutrition report.

inadequate release of protective material from exocrine glands, and decreased participation of the signaling pathway in serum proteins, albeit the underlying processes are unknown [25]. Children's intrinsic and innate immune responses are also influenced by protein and micronutrient deficits [26]. In children, changes in the gut microbiota can limit growth, disrupt inflammatory immunological processes, reduce functional brain connections, and also delay psychomotor and intellectual abilities [27, 28].

Other geriatric syndromes have been associated with depressive symptoms and malnutrition, both of which are modifiable risk factors for 30-day readmission in hospitalized older people [29]. The prevalence of malnutrition, as measured by the CONUT score, was high in older people undergoing elective surgery for colon cancer patients. Malnutrition has been related to a prolonged stay in the hospital as well as a higher chance of negative outcomes. Both death and readmissions to the intensive care unit are on the rise. CONUT is a quick and easy nutritional screening test that has previously been used to assess nutritional status in people who have had CRC surgery. A longer hospital stay is linked to a lower nutritional state. It's more likely that difficulties may occur. as well as a higher mortality risk [30]. Sarcopenia, cachexia, diminished sensory function, and alterations in the gastrointestinal system are some of the factors linked to old age [31].

3. Malnutrition in Pakistan: consequences

In South Asian nations, the primary factors of malnutrition and stunting are remarkably similar. The key categories include food insecurity and insufficient nutritional intake, social status and inequality, maternity and environmental factors, poverty, and water sanitation hygiene.

3.1 Inadequate dietary intake and food insecurity

Poverty and food insecurity are the two most persistent and major variables that cause stunting. Food insecurity affects children's nutrition, growth, and cognition and is a serious problem in developing nations. Food insecurity and diet variation should be considered while establishing strategies, plans, and interventions to address the problem of undernutrition [20]. The potential for economic growth of a country can impact food insecurity and, subsequently, the frequency of child stunting [32]. In Pakistani children, food insecurity is a major contributor to their low nutritional condition. In Pakistan, about two-thirds of families with nearly 80% of children lack adequate access to good and nutritional foods [33]. Insufficient diet, anemia, and nutrient deficits in pregnant mothers have been linked with lower childbirth weights in Pakistan. Even though Pakistan is a significant producer of rice and wheat becoming a food supply state, the nation's economic insecurity has exacerbated the nutritional inequality among children and babies. According to the Pakistan Economic Survey 2018–2019, Pakistan's overall food output and accessibility to basic food items are sufficient to meet the population's nutritional needs [34].

According to the Journal of the American Dietetic Association 3, in 2025, the supply of calories from key food groups per person would climb to 2530 calories. As per the Pakistan Cost of Diet Analysis, 67% of Pakistani families cannot afford a scientifically appropriate meal, while around 5% cannot afford a diet that fulfills even the necessities of energy needs [35]. Despite rising per capita wealth, increased food production and accessibility, and better intakes of gross energy (calories from food), Pakistan's current child stunting incidence is 40.2%. Nevertheless, over 60% of the people themselves are affected by food insecurity, with the lowest and perhaps most susceptible individuals in particular unable to buy sufficient healthy food [36]. Despite this, little is known about the non-nutritional repercussions of food insecurity, such as its implications on brain development and cognitive impairments, especially in developing countries [37]. The likelihood of baby undernourishment has also been connected to poor maternal mental health. Women with prenatal indicators of distress who lived in rural parts of Pakistan, and they had smaller amounts, larger family debts, and were food insecure, exhibited severe depression than women in high-income nations [38]. Young children are going through a phase of rapid growth and development, which necessitates more energy consumption. Humans and caretakers, on the other hand, meet their nutritional and dietary requirements. As a result, they are more likely to become malnourished [39]. Long-term exposure to natural disasters like landslides causes a decrease in the food supply, a lack of access to safe and nutritious food, a decrease in the quantity and quality of food consumed, and a lack of access to health, safe water, and sanitation facilities, all of which contribute to child malnutrition [40]. Long-term exposure to natural disasters, such as landslides, causes a decrease in the food supply, a lack of access to safe and nutritious food, a decrease in the quantity and quality of food consumed, and a lack of access to health, safe water, and sanitation facilities, all of which contribute to child malnutrition [41].

3.2 Socioeconomic status and disparities

There is a strong relationship between several indicators of socioeconomic status (SES) and child stunting in low- and middle-income countries (LMIC). Children's stunting is said to be impacted by socioeconomic inequity. Children in rural regions of the Democratic Republic of the Congo (DRC) were found to have a greater frequency of stunting than those in city environments. Boy stunting was much higher than girl stunting, especially among boys from low-income families. Breastfeeding, along with other nutrition treatments, must be given prompt attention to prevent stunting, they said [42]. Parents' educational levels, particularly mothers', mothers' health and nutritional status during pregnancy and lactation, children's vaccinations, family income level, and the current system were all socioeconomic factors affecting the nutritional health of children under the age of five in Nigeria [43, 44].

Stunting and thinness in Pakistani primary school kids (5–12 years) in Lahore, Pakistan, were studied for frequency and socioeconomic determinants. Researchers discovered that 8% of children were stunted and 10% were underweight, with no gender differences. Both boys and girls showed signs of stunting as they grew older, but only males were skinny. Stunting and thinness were found to be influenced by age, socioeconomic status, parental education, the number of siblings, overcrowding, and living in a smoky environment. Children from poorer, less qualified families who lived in low-income neighborhoods and in cramped residences with a smoking culture were considerably more likely to be stunted and skinny. Programs aiming at the disadvantaged and socially marginalized should be prioritized [45]. Stunting, underweight, and waste were identified in 44.4%, 29.4%, and 10.7% of Pakistani children (0–59 months), respectively. Mothers of children were under the age of 18 at the time of marriage, resided in rural regions, and attended a maternity clinic at least 3 times during pregnancy had a low risk of being stunted. Underweight in children was strongly linked to the mother's level of education, height, BMI, and birth weight. Investigators concluded that the majority of the variables that cause malnutrition in Pakistani children may be avoided [46]. A higher amount of income or wealth, on the other hand, has been linked to a lower incidence of malnutrition in children. As a consequence, Pakistani women's empowerment can help improve people's health, which is key for the country's future progress [47]. Parents with a lower degree of education have a lower household income and are more likely to live in poverty. They spend less money on appropriate nutrition because of a shortage of food, basic health care services, and exposure to terrible living conditions and diseases, and their children are more prone to growth failure [48].

3.3 Poverty

Many of us associate poverty with pictures of starvation or children dying from avoidable diseases on television from the poor world [49, 50]. Poverty is a multifaceted issue in Pakistan. It is firmly embedded in the social, economic, and political systems of the country. The lack of good economic and political governance is the greatest obstacle to poverty reduction. Poverty was once associated with the severe types of malnutrition, particularly in children, that were common during times of famine and starvation. As indicated in **Figure 2**, the World Bank utilized the lower-middle-income poverty rate ($3.2 per day) to predict that Pakistan's poverty rate stood at 39.3% in 2020–2021, is expected to continue at 39.2% in 2021–2022, and may drop to 37.9% by 2022–2023. Impoverished individuals are more susceptible to natural dangers (lack of sanitation, inadequate food, crime, and natural disasters), are far less aware of the benefits of good health, and get less access to quality health care. As a result, individuals seem to be more prone to disease and disability [51]. When girls reach reproductive age, they are more likely to give birth to low-birth-weight babies, who have a worse chance of survival than typical babies. Undernutrition is one of the most frequent diseases, the major cause of inadequate healthy development, and by far the most important component inhibiting a country's progress [52].

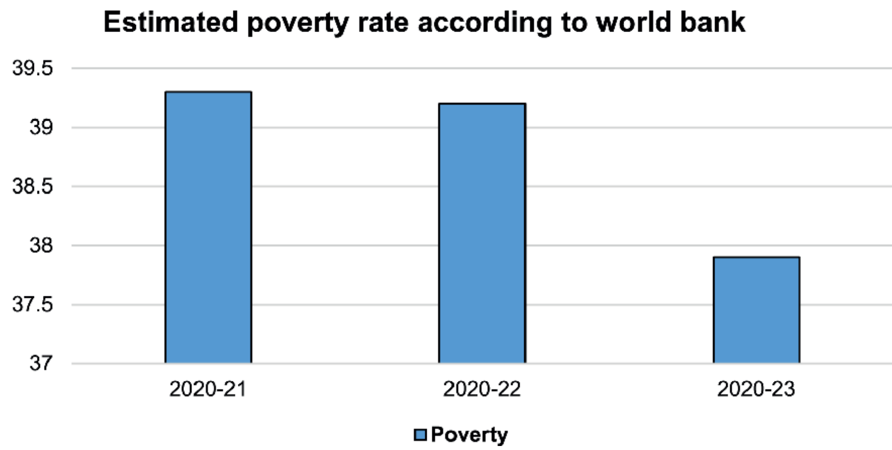

Figure 2.
Poverty rate from 2020 to 2023.

3.4 Maternal and environmental factors

Malnutrition and stunting in children are generally induced by several factors, namely maternal health, ecological and home circumstances, poverty, socioeconomic disparities, low birth weight, dirty water, sanitation, proper hygiene, infections, and diarrhea [53, 54]. Gastrointestinal tract damage, immune suppression, including liver illness across both mothers and infants, as well as stunting in children, are all linked to aflatoxin and mycotoxin exposure from contaminated food [55]. Children who grow up in agricultural areas tend to have development problems throughout pregnancy, childhood, and adolescence [56]. The use of polluted water and the early introduction of supplemental feeding raises the risk of infections and water-borne illnesses including diarrhea and cholera, which impairs children's food intake and nutrient utilization, causing stunting and wasting [57].

3.5 WASH (water, sanitation, and hygiene)

Poverty, poor sanitary conditions, and dirty water are the causative factors of child retardation in Pakistan, by a World Bank study. In Pakistan, open latrines are widely used, and the country is ranked third in the world for open defecation. Many nutritional and health issues are linked to open latrines, including intestinal infection and disease transmission. In Sindh, water and soil polluted with *Escherichia coli* are detected in greater quantities than in Punjab [58]. This is due to an insufficient sewage disposal system and inappropriate human waste treatment. The feces-infected water enters the irrigation system, causing tainted crops to grow that are unsafe to eat. Because of too much access to intestinal parasites, poor drainage, sanitation, and sanitary circumstances influence children's growth and development. On-diarrheal sickness and death in children can be reduced by using nutritional, therapeutic, and behavioral strategies [59]. **Figure 3** depicts the effect of household income on energy intake, which results in anthropometric measurements of stunting and wasting. If one's calorie intake is less than one's energy expenditure, it leads to physical inactivity and makes it difficult to work as an adult. All of these factors have an impact on health, resulting in illnesses. This clarifies the relationship between economy,

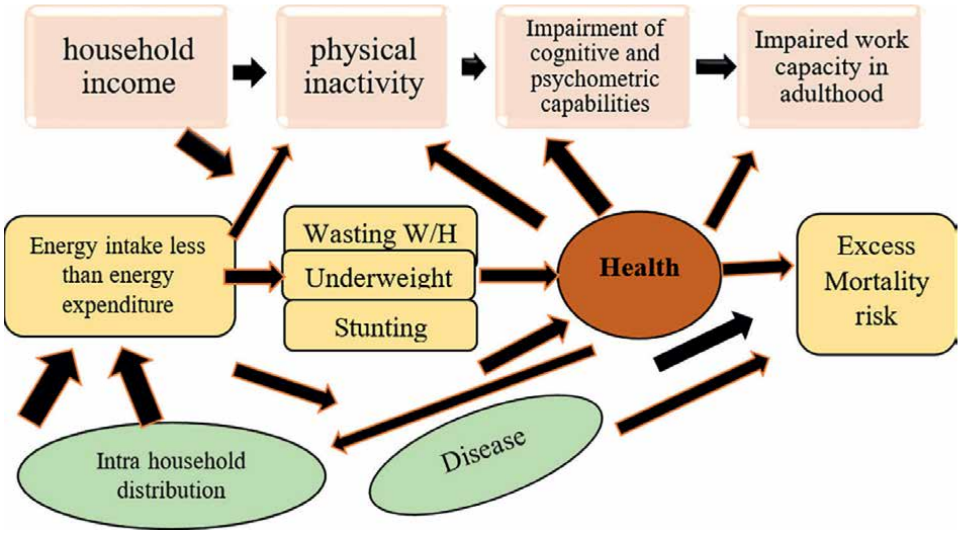

Figure 3.
Consequences of undernutrition.

nutrition, and health. In children, *E. coli* causes environmental enteric dysfunction (EED), which causes profuse diarrhea. In underdeveloped nations, EED suppresses the immune system, impairs children's cognitive and mental development, causes growth retardation, and causes malnutrition [60, 61].

Inadequate toilet facilities, inadequately treated water supplies, underprivileged healthcare access in remote regions, diarrhea and diseases, and food insecurity are among the most powerful factors of malnutrition and stunting in children in the developing world, according to the above-mentioned data.

3.6 Strategies to cover malnutrition

The eradication of child malnutrition is crucial for people's and society's development. To achieve zero stunting, thorough nutritional therapy regimens must be implemented, particularly during the first 2 years of life. Multi-targeted intervention strategies with a focus on growth and anthropometric parameters are advised. Reduced child stunting is a crucial aim in reaching zero hunger, according to the Global Nutrition Targets for 2025 [62]. Scaling Up (SUN) The need to include stunting prevention in all future sustainable development efforts undertaken by member nations is highlighted by nutrition. Poor nursing habits and dietary deficiencies are thought to be the primary health issues of child stunting and bad health. Pakistan should promote supplementary feeding services for kids above the age of 6 months in addition to exclusive breastfeeding. To boost the nutritional impact of supplementary feeding habits and enhance children's nutritional status, recommendations on their entry timing and frequency must be created and executed. It is necessary to develop and deliver suitable, low-cost fortified supplemental nutritious meals that are compatible with unique cultural foods, especially to homes at risk of potential poverty. According to the Global Alliance for Improved Nutrition, the leading causes of stunting in children are premature marriages and breastfeeding females more than boys. Boys are often given more food than girls, resulting in stunting and malnutrition in the female population. Not only are they unable to compete in many sectors with males, but malnourished moms are also unable to give birth to healthy kids [63].

Cooperative efforts to improve maternal nutrition and to eliminate child stunting, focusing on a variety of actions in areas such as agriculture, the environment, water, sanitation and hygiene, schooling, poverty alleviation, and social welfare, including the implementation of specific laws and policies. In Pakistan, malnutrition must be seen through an ideological lens, with implications for overall growth [64]. Cross strategies including all dietary and micronutrient techniques, to eliminate hunger and childhood stunting in Pakistan, strong political will must be formed and enforced. Deprivation, food shortages, bad sanitation, and hygienic practices, disease infection and vulnerability, maternity care, inequalities gender issues, poor diet patterns, and poor diets, as well as a high population growth rate, increasing urbanization, sensitivity to protection and wellbeing situations, or an absence of adequate ideological would all add to the quality of Pakistan's dietary difficulties. According to the findings of a recent study, the majority of these variables are avoidable. On the other hand, integrated solutions for addressing these concerns should be developed in the framework of society's academic and nutritional efforts [46]. Nutritional therapies can reduce stunting in general. Stunting is a significant danger for children living in urban slums. When creating dietary approaches to reduce low birth weight and child retardation in these kinds of circumstances, the diversity of such conditions in terms of physiological, social, and economic elements should be acknowledged [65]. It's vital to create well-designed coordinated multistakeholder intervention strategies which use rational ways to fulfill the requirements of the most desperate individuals that are more prone to stunting as poverty [66]. As a result, appropriate recommendations initiatives should not only aim to reduce poverty, undernourishment, and climate difficulties but also improve and maintain a lengthy economic growth goal within the native culture. Because nutritional deficiencies, like iron and iodine, can harm children's brain growth early in life, nutritional supplementation throughout pregnancy and childbirth is crucial for preventing cognitive deficits in infants and children [67]. Stunting and malnutrition can be reduced by food adjustments such as food supplements and micronutrient replacement, in combination with diet therapies [68, 69]. Niazi concluded that governmental and non-governmental institutions' nutritious prevention efforts in Pakistan failed to deliver their aimed nutrition outcomes because they did not take an incorporated way of tackling the important principles of malnutrition such as lack of education, economic hardship, and sociocultural deprivation [70]. Every year, stunting among children causes Pakistan to lose 3% of its GDP. It is projected that every rupee spent to combat malnutrition will provide a return of 16 rupees. Well-fed children have a 33 percent higher chance of escaping poverty as adults [71, 72]. If adequate intervention programs and policies are adopted, Pakistan may likewise address the problem of malnutrition and stunting.

3.7 Malnutrition alleviation and economic growth

The link between economic advancement and improved nutrition can be either positive or negative. As per Wang and Taniguchi, good nutrition is beneficial to protracted income progress, although the benefits could be hidden by a current rapid population surge [73]. Headey investigated the effects of economic growth on dietary stunting in middle- and low-income nations across three continents. Increased food availability, poverty alleviation, and enhanced maternal and child health care, he claims, are all positives [74]. Nonetheless, even within areas, the nutritional impacts of economic expansion vary greatly. Thus according to conventional anthropometric measures, the incidence of malnutrition declined little in Sub-Saharan Africa despite decades of Economic growth faster than the overall. She also noted substantial differences in the distribution of child nutrition increases among demographic categories (such as urban vs. rural) [75].

4. Early (indirect) intervention: nutrition-sensitive programs

Despite having multiple primary goals, nutrition-sensitive programs could have a similar impact on the underlying cause of child malnutrition as 'micronutrient' initiatives, not only as they are more diverse and larger in scale. Nursing and parental leave laws, free iron and folic acid for pregnant women, and vitamin A for early children are all examples of national programs [76]. Farming, healthcare, social welfare, early education, schooling, irrigation, and cleanliness are among the numerous sectors participating in nutrition-sensitive initiatives [77]. Conditional cash transfers are currently one of the most researched & examined types of planned action [76]. A sort of dietary approach provides financial assistance to individuals and households in need, often in exchange for a reciprocal activity like school attendance or completing a vaccination regimen. Although its main objective is to eliminate misery, such as in an emergency, there is increasing support that they have huge development influence [78].

Figure 4 depicts interventions that would reduce child malnutrition. Various organizations are collaborating with the UN to combat hunger, malnutrition, food insecurity, and other problems. WHO (World Food Organization), FAO (Food and Agriculture Organization), SUN (Scaling up Nutrition), UNHCR (United Nations High Commission for Refugees), and others are among these bodies. Each group devised its strategy to address the issue of malnutrition, which we will examine

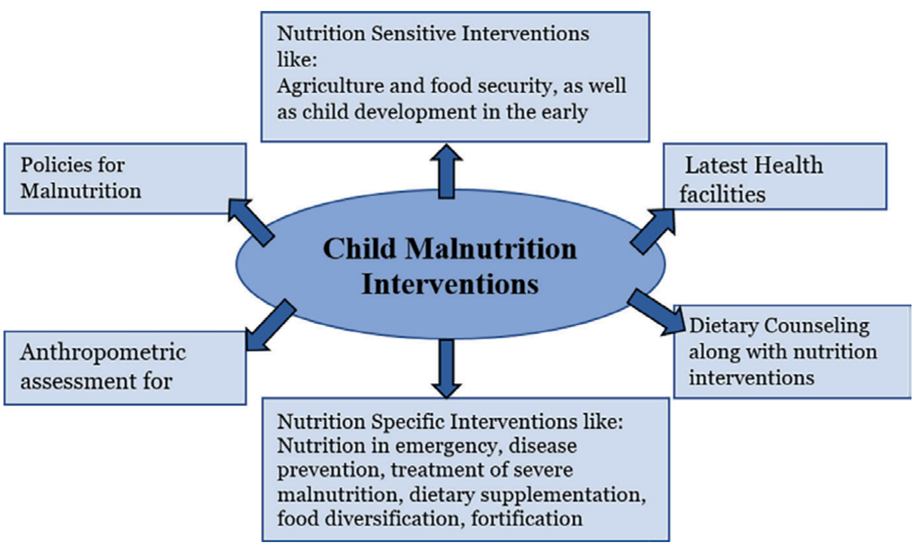

Figure 4.
Strategies for child malnutrition.

below. More Money for Nutrition and more nutrition for money (according to SUN Movement Strategy 2021–2025).

- Bringing together the efforts of several groups
- Providing food helps developing and underprivileged nations
- Developed policies for displaced and refugee populations who are particularly prone to hunger
- Checking and balancing the consequences for governance operations (according to SUN Movement Strategy 2021–2025)
- Make wheat, which is Pakistan's key food item, available to all of the country's citizens.
- Tracking Tools to assist nations in determining and monitoring their national objectives (FAO strategy)
- Breastfeeding should be encouraged to avoid nutritional deficits in newborns.

5. Conclusion

Malnutrition is one of the world's most serious health problems, affecting about 2 billion people. UNICEF/WHO/World Bank Group estimates that 151 million children under the age of five are stunted, 50 million are wasted, and 17 million are severely wasted, according to UNICEF/WHO/World Bank Group estimates. Malnutrition is prevalent in Pakistan. Food insecurity, poverty, sanitation, hygiene, maternal and environmental variables, education, stunting, and other factors all contribute to malnutrition. This might be due to inadequate or ineffective intervention policies and programs, which have tended to focus on a single issue at a time rather than employing multi-sectoral methods to address the various factors that contribute to stunting. Cost-effective multitier interventions must be administered during the preconception, prenatal, and especially early postoperative periods to prevent malnutrition, stunting, and wasting in children. It is suggested that a comprehensive plan be devised and implemented to address the problem of malnutrition and stunting, which includes nutrition and WASH treatments, as well as activities to improve socioeconomic status. To guarantee that particular projects are created, performed, and sustained promptly, legislators, government and non-government agencies, other parties, and, most importantly, individual contributions and support are required.

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Conflict of interest

There is no conflict of interest.

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Chapter 8

Perspective Chapter: Early Diagnosis of Malnutrition

Tomiyo Nakamura and Hiroshi Imamura

Abstract

Low body mass index (BMI) and unintentional weight loss are the criteria used in many nutritional screening tools (NSTs) to identify the nutritional status of patients and the elderly. However, in hospitals, nursing homes, and communities, weight is often unmeasured. Therefore, we researched the current situation of inadequate nutritional screening due to a lack of weight measurements and what should be done to improve this situation. We conducted a narrative review of peer-reviewed research on nutritional screening, NSTs, missing NST parameters, regular weight measurements, awareness of malnutrition among physicians and others, and nutrition support based on PubMed and J-stage. The NSTs included mostly weight or weight-based parameters (BMI and weight loss). Our findings suggest that, since patients and the elderly do not weigh themselves regularly, they are unaware of their weight loss and do not receive proper nutritional care. The results also show that physicians do not often recognize nutritional problems that require nutritional intervention and do not order nutritional intervention by dietitians. Moreover, patients and community residents at risk of malnutrition do not recognize anorexia and weight loss as nutritional problems. Multidisciplinary and collaborative nutritional interventions are needed to reduce the risk of malnutrition in patients and the elderly.

Keywords: malnutrition, weight loss, nutrition screening, nutritional intervention, weight measurement

1. Introduction

Malnutrition in patients and the elderly decreases the activities of daily living and the quality of life, and it contributes to infections and delayed healing due to reduced immunity, which affects patient prognosis and survival [1]. Therefore, it is important to identify malnutrition at an early stage and provide appropriate nutritional care.

A variety of nutritional screening tools (NSTs) have been developed to identify malnutrition in patients and the elderly, and many tools and their diagnostic accuracies have been reported [2–6]. The parameters of NSTs are generally categorized into anthropometric, biochemical, clinical, dietary assessment, psychological, social, and physical parameters [7]. Most NSTs include anthropometric measurements, especially weight and weight-based parameters (body mass index [BMI] and weight loss).

The Global Leadership Initiative on Malnutrition (GLIM), developed in June 2018 with the participation of four societies in Europe, the United States, Asia, and

South America, suggests the evaluation of the possibility of malnutrition by assessing phenotypic and etiologic criteria if a validated screening tool determines a patient is at risk [8]. The phenotypic criteria are (1) unintentional weight loss, (2) low BMI, and (3) reduced muscle mass, and the etiologic criteria are (1) reduced food intake or assimilation and (2) inflammation or disease burden. If any of these phenotypic or etiologic criteria are met, a diagnosis of malnutrition is established, and the severity is proposed according to phenotypic metrics. Thus, low BMI and weight loss are not only NSTs, they are also essential components of the GLIM criteria and are equal or more important nutritional parameters compared with other measures of nutrition. Therefore, if the weight of patients and elderly people are not measured and low BMI and unintentional weight loss are not assessed, there is a possibility that truly undernourished patients will not be identified.

Low BMI and unintentional weight loss are the criteria used in many NSTs to identify the nutritional status of patients and the elderly. Unintentional weight loss, a characteristic of malnutrition, is associated with a loss of skeletal muscle mass and increases the risk of sarcopenia, which is characterized by a loss of both muscle mass and muscle strength and function [9]. For this reason, it is important to identify unintentional weight loss.

However, in hospitals, nursing homes, and communities, bodyweight, which is required for evaluating nutritional parameters such as low BMI and unintentional weight loss, is often not measured [10–12]. This has led to the inadequate nutritional screening of patients and the elderly and has caused cases of malnutrition to be overlooked. Therefore, we researched the current situation of inadequate nutritional screening due to the lack of weight measurements to identify strategies to improve this situation.

We conducted a narrative review of peer-reviewed research on nutritional screening, missing NST parameters, regular weight measurements, awareness of malnutrition among physicians and others, and nutrition support from 2010 to 2021 using PubMed and J-stage [13]. Regarding NSTs, the major ones are listed, without any limitations on date.

2. Major validated nutritional screening tools

This section reviews the parameters for assessing the nutritional status of major validated NSTs. Nutritional screening is the first step in nutrition management. A validated NST should be used to identify patients and older adults at nutritional risk, perform a nutritional assessment, and initiate an appropriate intervention for nutrition support.

A systematic review of NSTs for the hospital setting identified 32 different NSTs, most of which were reported to include low BMI and weight loss [14]. Another systematic review reported that 16 NST parameters were categorized as anthropometric, biochemical, clinical, dietary assessment, psychological, social, and physical parameters [7]. In the NSTs, 93% included physical measurements, especially weight or weight-based parameters (BMI and weight loss), and only 12% included biochemical parameters [7]. The commonly NSTs used are described below [2–6].

1. Malnutrition Screening Tool (MST)

   The MST is a simple tool designed by Ferguson et al. which inquires only about weight loss and appetite loss [2].

2. Malnutrition Universal Screening Tool (MUST)

   MUST is an NST developed by the British Society of Venous and Enteral Nutrition [3]. The total score of four items (BMI, weight loss, acute illness, and inadequate nutritional intake) is used to determine low, medium, or high risk.

3. Nutritional Risk Screening 2002 (NRS2002)

   NRS2002 is an NST developed by the European Society for Clinical Nutrition and Metabolism in 2002, and it is mainly used in acute care [4]. It consists of an initial screening consisting of four items: BMI, weight loss, decreased dietary intake, and the presence of severe disease, and a final screening consisting of nutritional impairment, disease severity, and age-related scores.

4. Mini Nutritional Assessment Short-Form (MNA-SF)

The Mini Nutritional Assessment (MNA) was developed to evaluate certain subgroups, especially the elderly, before overt changes in weight or albumin occur [5]. The MNA-SF was later designed to provide a simpler and more practical screening tool [6]. It consists of six items. Each indicator is scored from 0 to 2 or 3, and the total score is used to determine whether the patient has a normal nutritional status, is at risk of malnutrition, or is malnourished.

	MUST	**NRS2002**	**MNA-SF**
BMI (kg/m^2)	0: ≥20 1: 18.5–20 2: ≤18.5	1: 18.5–20.5 2: ≤18.5	3: ≥23 2: 21–23 1: 19–21 0: ≤19
Weight loss	(in the past 1–6 months) 0: ≤5% 1: 5–10% 2: ≥10%	1: ≥5% in 3 months 2: ≥5% in 2 months 3: ≥5% in 1 month	(During the last 3 months) 3: no weight loss 2: 1–3 kg 1: does not know 0: ≥3 kg
Food intake	2: acutely ill + no nutritional intake for > 5 days	0: 0–25% 1: 25–50% 2: 50–75%	2: no decrease 1: moderate decrease 0: severe decrease
Mobility			0: bed or chair bound 1: able to get out of bed/chair but does not go out 2: goes out
Psychological stress or acute disease			(Within the past 3 months) 2: no 0: yes
Neuropsychological problems			2: no psychological problems 1: mild dementia 0: severe dementia or depression

BMI, body mass index; MUST, Malnutrition Universal Screening Tool; NRS2002, Nutritional Risk Screening 2002; MNA-SF, Mini Nutritional Assessment Short-Form.

Table 1.
Screening scores for each indicator in the major nutritional screening tools.

Table 1 shows the screening scores for each indicator in the three NSTs. All three NSTs assess weight loss, BMI, and food intake. In these three NSTs, only MNA-SF can be assessed even if weight loss is unknown. The duration and amount of weight loss for the three NSTs are not standardized, but a weight loss of 5% within 3 months may be the standard.

Thus, the parameters of NST include mostly weight or weight-based parameters (BMI and weight loss). This suggests the importance of regular nutritional screening and regular weight measurements for identifying malnutrition.

However, some patients and the elderly are unable to measure their own weight. Therefore, the advantage of the MNA-SF is that it can measure the calf circumference (CC) instead of BMI for elderly people who have difficulty measuring their height and weight [6]. However, Kostka et al. evaluated the usefulness of the MNS-SF in different elderly populations in Poland and concluded that BMI is more useful than CC [15]. For this reason, CC should be used only when BMI cannot be measured, and weight should be measured when possible.

Author, Year	NST	Subjects	Missing parameter data
Hospitals			
Neelemaat F., 2011 [10]	MUST MNA-SF	Netherlands (n = 275)	Missing data 47% 41%
Henriksen C., 2017 [16]	ESPEN [17]	(nDay survey) Norway (n = 488)	BMI: weight or height missing 1/3
Ostrowska J., 2021 [18]	MST	(nDay survey) Poland European	Weight loss: missing/unknown 64% (n = 496) 64% (n = 10,862)
Nursing homes			
Graeb F., 2021 [11]	MUST	Germany (n = 2,058)	Previous weight or no weight Some residents
Torbahn G., 2021 [19]	17 variables	European (n = 39,840)	No data for body weight at follow-up 51.3%
Communities			
Lahmann N. A., 2016 [12]	MNA-SF MUST	Germany (n = 878)	Weight loss: missing/unknown 48.8% 39.1%
Nakamura T., 2021 [20]	Japan NST	Japan (n = 103)	Weight loss: missing/unknown 78.6%
Mikkelsen S., 2021 [21]		(Interviews) Denmark (n = 30)	Health professionals rarely saw patients with unintended weight loss

BMI, Body Mass Index; MUST, Malnutrition Universal Screening Tool; ESPEN, European Society for Clinical Nutrition and Metabolism; MNA-SF, Mini Nutritional Assessment Short-Form; NRS2002, Nutritional Risk Screening 2002; NST, Japan Nutritional Screening Tool; nDay Survey, nutritionDay Survey.

Table 2.
Screening scores for each indicator in the major nutrition screening tools.

3. Deficiencies in nutrition screening parameters

This section reviews the proportion of patients and residents assessed by NST-based nutritional screening in hospitals, nursing homes, and the community. **Table 2** shows the screening scores for each indicator of the major NSTs.

Neelemaat et al. compared five MSTs for patients in one hospital and found that 47% of the data were missing for MUST and 41% were missing for MNA-SF [10]. They also reported that MUST had low applicability due to the high rate of missing data, while the MNA-SF showed excellent sensitivity but low specificity.

Henriksen et al. attempted to quantify the frequency of malnutrition and the proportion of malnourished patients in two university hospitals in Norway using data from the nDay survey [16]. However, they reported that BMI could be calculated for only two-thirds of the patients because weight and height data were often missing from the patient records.

Ostrowska et al. compared results from all European countries participating in the nDay survey with those from Poland [17]. The results showed that 64% of the data on weight loss within 3 months were missing in both Europe and Poland, and several elements of the nutritional management process in Polish hospitals were inadequate. These results indicate that not all hospital inpatient weight data are available.

Graeb et al. analyzed data from a total of 2058 residents of 19 nursing homes who were hospitalized for more than 3 days in order to determine the causes of their malnutrition risk [11]. The results suggested that the actual prevalence of malnutrition and the risk of malnutrition may still be underestimated, as the last weight measured was a long time ago and some residents did not have access to their weight history prior to hospitalization.

Torbahn et al. investigated predictors of malnutrition in nursing home residents aged 65 years and older who participated in the nDay survey from 2007 to 2018 [19]. They excluded 20,443 (51.3%) of the 39,840 residents with no data on bodyweight at follow-up. This study shows that most nursing homes do not regularly measure the weight of their residents.

Lahmann et al. conducted a multicenter prevalence study of 878 randomly selected clients from 100 randomly selected home care services in Germany in 2012 [12]. They reported that there were many missing values in both NSTs (MNA-SF 48.8%, MUST 39.1%) because many clients did not provide information on weight loss over the past 3–6 months. This finding also emphasizes the need for home care clients to be weighed on a regular basis, so that potential weight loss can be identified early.

Nakamura et al. conducted nutritional screening of the community's elderly at a daycare facility, but 79% of the participants had no past weight history and their weight loss could not be calculated [20].

Mikkelsen et al. analyzed individual semi-structured interviews of general practitioners and focus group interviews of clinic nurses [21]. They reported that general practices did not routinely identify disease-related malnutrition and rarely saw patients with unintended weight loss.

The results of these studies suggest that many elderly and chronically ill patients in the community do not weigh themselves regularly, are unaware of their weight loss, and do not receive appropriate nutritional care.

Table 3 shows the routine weight measurements in hospitals and nursing homes.

Author and Year	Subjects	Routine weight measurements
Hospitals		
Cereda E., 2010 [22]	(Project: Iatrogenic Malnutrition) Italy (n = 1,583)	BMI (38.2%) Nutritional support (13.6%) Weight monitoring (21.6%)
Ostrowska J., 2021 [18]	(nDay survey) European vs. Poland (n = 10,862) (n = 496)	At hospital admission (100% vs.72.9%) Weekly (20% vs.41.4%) Occasionally (0% vs. 9.2%)
Communities		
Lahmann N. A., 2016 [12]	Germany 100 home care services	33.6–57.3%

BMI, Body Mass Index; nDay survey, nutritionDay Survey.

Table 3.
Routine weight measurements in hospitals and home care services.

Cereda et al. reviewed the data on nutritional care routines collected in the Project: Iatrogenic MAlnutrition in Italy (PIMAI) study [22]. The results showed that only 38.2% of the patients had their BMI calculated based on their care in the wards. Nutritional support was prescribed only in 26/191 (13.6%) patients who presented with obvious malnutrition. In addition, only 21.6% of patients had their weight monitored according to a schedule. They concluded that the routine of nutritional care in Italy is still poor and needs to be improved.

Ostrowska et al. compared results from all European countries participating in the nDay survey with those from Poland and found that the patients' weight was recorded on admission (100% vs. 72.9%; $p < 0.0001$), weekly (20% vs. 41.4%; $p < 0.05$), and occasionally (0% vs. 9.2%) [18].

Lahmann et al. reported that the rate of routine weight measurement in 100 homecare services in Germany ranged from 33.6% to 57.3% [12]. These findings suggest that not many of the elderly people living in the community are weighed on a regular basis.

Reports indicate that 89% of dietitians use weight to solve nutrition problems in malnourished community members, and 87% use BMI as an outcome measure for successful nutritional intervention [23]. Furthermore, regular weight measurements are essential for successful nutritional screening and interventions by dietitians in order to solve the nutritional problems of community residents.

4. Awareness of malnutrition, nutritional screening, or nutrition support

This section reviews the perceptions of healthcare providers, staff, patients, residents, and families toward malnutrition, nutritional screening, and nutrition support. We performed a PubMed search using the keywords malnutrition, nutrition screening, nutrition support, and awareness. The results are shown in **Table 4**.

Author and Year	Subjects	Awareness
Healthcare professionals and staff		
Caccialanza R., 2016 [1]	Oncologists (n = 2375) Patients (n = 66) (Italy)	Participation 135 (5.7%) Nutritional assessment: only at the patients' request (n = 62)
Deftereos I., 2021 [25]	130 participants (56% dietitians, 25% surgeons, 11% nurses, 8% oncologists) (Australia)	Dietetics support (98%) Outpatient service (41%)
Morimoto T., 2020 [26]	Oncologists (n = 500) (Japan)	Loss of appetite Interventions for weight loss: Dietary guidance (49.8%)
Patients and Community-dwelling people		
Avgerinou C., 2019 [27]	Community-dwelling people aged ≥75, identified as malnourished or at risk of malnutrition (n = 24), and informal caregivers of older people (n = 9) (UK)	Nonrecognition of lack of appetite and weight loss as problems
Morimoto T., 2021 [26]	Patients (n = 538) Their family (n = 517) (Japan)	Lack of appetite: Patients (29.0%) Their family (56.5%) Weight loss: Patients (38.3%) Their family (46.4%)

Table 4.
Awareness of malnutrition, nutritional screening, and nutrition support.

Caccialanza et al. noted that there may be a lack of awareness and consideration of nutritional issues among oncologists in Italy, as only 5.7% of the 2375 members participated in the survey [24].

Deftereos et al. conducted a national survey of clinicians with the goal of identifying interdisciplinary clinician practices, perceptions, and perspectives on screening for malnutrition and providing nutritional support for patients undergoing surgery for upper gastrointestinal cancer [25]. The results showed that most participants reported that overall dietary support was available at their healthcare service (98%), but only 41% reported it was available through outpatient services.

Morimoto et al. conducted a web-based questionnaire survey of 500 oncologists [26]. Among the responses, the most common causes of anorexia and weight loss were symptoms due to systemic inflammation caused by cancer (58.8%), and the second most common cause was side effects of anticancer drugs (49.0%). The most common intervention was the prescription of antiemetics (69.7%), and the second most common intervention was teaching patients how to eat recommended foods (49.8%).

Avgerinou et al. conducted a qualitative study using semi-structured interviews to investigate the views of community-dwelling older adults and their caregivers regarding the management of malnutrition [27]. The results showed that older adults at risk of malnutrition rarely recognized lack of appetite or weight loss as a problem.

A web questionnaire survey of cancer patients by Morimoto et al. reported that 38.3% of patients and 46.4% of family members stated they became concerned about weight loss only after a cancer diagnosis [26]. **Figure 1** shows the causes of weight loss during cancer treatment based on patients' perceptions. The patients considered the effects of surgery and the side effects of anticancer drugs as the two most common causes of weight loss.

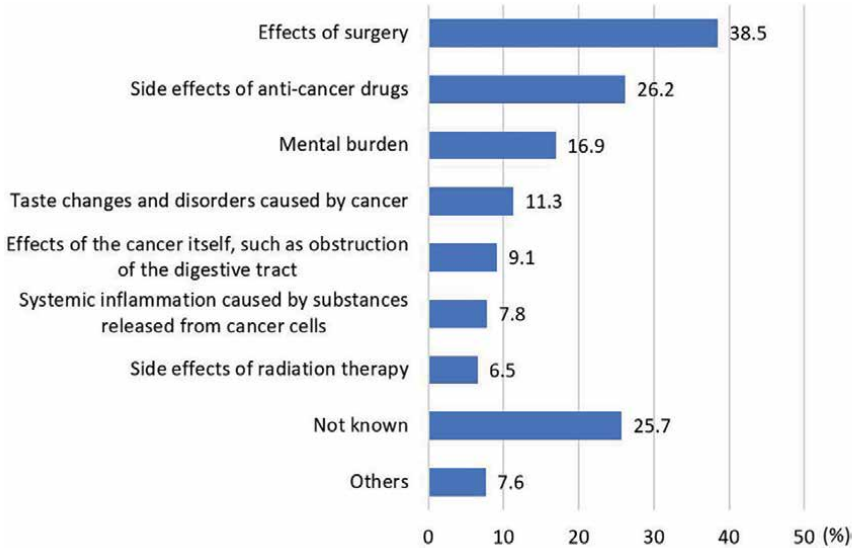

Figure 1.
Responses to a question to patients: "What do you think are the major causes of weight loss during cancer treatment?" (Multiple answers) (n = 538). (Adapted from [26]).

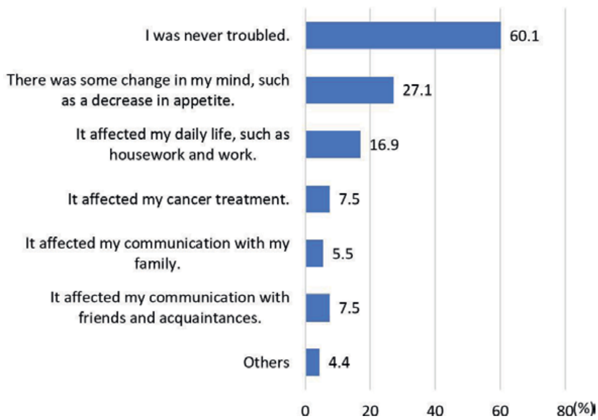

Figure 2.
Responses to a question to patients: "Do you have any trouble with weight loss? (Multiple answers) (n = 361). (Adapted from [26]).

Figure 2 presents patients' concerns about weight loss, and 60% of the patients responded that they were unconcerned. Morimoto et al. reported that 42.1% of the patients reported or consulted their doctors or nurses about their weight loss, while 66.5% of those who did not seek consultation reported that they did not think it was something to be concerned about.

These results indicate that physicians do not recognize nutritional problems that require nutritional intervention and do not order for nutritional intervention by dietitians and that patients and community residents at risk of malnutrition do not recognize anorexia and weight loss as nutritional problems.

5. Nutrition supports for preventing malnutrition

Despite the development of various NSTs and the provision of clinical guidelines recommending regular nutritional screening, malnutrition in patients and the elderly remain unrecognized because regular weight measurements, an integral part of nutritional screening, are not performed. To improve this, various nutrition interventions for staff and community residents have been considered. In this section, these nutrition interventions are presented.

Everink et al. compared the prevalence of malnutrition among nursing home residents in the Netherlands in 2009, 2013, and 2018 [28]. They reported that the prevalence of malnutrition was relatively stable at approximately 16% and that it was unclear whether nursing staff were adequately aware of malnourished (at-risk) residents and the interventions that could be implemented to reduce this occurrence.

Charlton et al. evaluated the adoption of a nutrition care model for older adults designed to improve the detection and management of malnutrition [29]. A systematic review aimed at assessing the effectiveness of nutritional interventions on frailty and frailty-related factors (e.g., malnutrition, sarcopenia, functional capacity) in community-dwelling older adults concluded that multifactorial interventions are more effective than nutritional interventions alone in improving frailty and physical performance [30].

A narrative review that aimed to identify practical conclusions to support the interdisciplinary management of malnutrition in cancer patients suggested that knowledge sharing between oncologists and dietitians can help to successfully address and treat malnutrition in this population [31].

Imamura et al. suggest that postoperative weight loss may affect chemotherapy compliance and may be a risk factor for survival [32]. They reported that patients receiving adjuvant chemotherapy with oral elemental nutritional supplements had increased treatment completion.

Considering these various nutritional interventions, it is necessary to improve the assessment and treatment of malnutrition in patients and the elderly.

6. Limitation

This chapter was a narrative review of peer-reviewed research on nutritional screening, NST, missing NST parameters, regular weight measurements, awareness of malnutrition, and nutrition support. However, only a few studies addressed the missing parameters, missing data, or lack of awareness itself. For this reason, relevant reports were examined one by one in detail, which could have led to a selection bias in the literature retrieved.

7. Conclusion

The findings of this research suggest that patients and the elderly do not weigh themselves regularly, are unaware of their weight loss, and do not receive proper nutritional care. The early diagnosis of malnutrition through routine weighing and nutritional screening and interdisciplinary and collaborative nutritional interventions are necessary to reduce the risk of malnutrition in patients and the elderly.

Conflicts of interest

The authors declare no conflicts of interest.

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Chapter 9

Malnutrition in the Elderly: A Recent Update

Aydan Çevik Varol

Abstract

Malnutrition is a common problem in the elderly. Malnutrition prevalence has been reported to be between 5 and 10% in elderly living at home and quite more in hospitilized ones. It has been observed that elderly people in need of home care services face malnutrition problems more frequently than general elderly population. Elderly people cared by home care services, especially when they have chronic, mental, or physical disease, they are inclined to be at a higher risk for malnutrition. If malnutrition is not detected and properly managed, it makes it difficult to treat other existing, clinical diseases. On the other hand, it causes increase of complications related to the patient and accordingly prone to higher morbidity and mortality risks. Therefore, all the elderly patients admitted to home care service have to be examined and evaluated for malnurtition risk and managed accordingly.

Keywords: elderly people, malnutrition, geriatric syndrome, nutrition, malnutrition treatment

1. Introduction

Although the term malnutrition has a meaning that includes the condition of being overweight, according to Early Career Faculty The European Society for Clinical Nutrition and Metabolism (ESPEN), it is defined as physical changes in body composition as a result of clinically significant malnutrition, as well as body functions and clinical outcomes [1, 2]. As a result of malnutrition mentioned here, it causes changes in body composition (decrease in fat free mass [FFM] and body cell mass [BCM]) that affect the physical and mental functions of the person and the healing process from diseases. In clinical practice, in addition to the decrease in food supply, increased catabolism in the body after trauma and inflammatory diseases also causes malnutrition. An important point here is that while malnutrition caused by inadequate food intake is easier to correct, the negative energy and nitrogen balance in the catabolic phase of diseases cannot be reversed even with large amounts of food intake. Replacing the lost tissues is only possible by controlling the inflammation [3, 4]. For these reasons, when evaluating the risk of malnutrition in individuals, static measurements such as body mass index (BMI) and anthropometry are evaluated together with simple bedside measurements of disease severity and body functions (e.g., evaluation of mood, hand-wringing dynamometer, measurement of peak expiratory flow) [5]. According to this information, the definition of malnutrition is a combination of both excessive and insufficient nutrition and inflammatory activity, and it is defined as a subacute or chronic nutritional disorder that causes changes in body composition and loss of functions [6]. Both definitions can be considered valid and should probably be used together because it is important for a definition to have a therapeutic feature to guide the clinician to select patients who would benefit from nutritional therapy. The process of identifying patients with nutritional problems begins with a rapid screening and continues with a detailed evaluation of those found to be at risk [7].

To diagnose an individual as being malnourished, two or more criteria of those need to be fullfilled: i) low energy intake, ii) weight loss, iii) loss of muscle mass, iv) loss of subcutaneous fat, v) fluid accumulation, and vi) hand grip [8]. Malnutrition is reported to be related with cognitive functioning in the elderly [9]. In addition, it is used to predict morbidity and mortality rate after surgical operations in critical elderly cases [10]. Also, it was shown that malnutrition increased the risk of readmission in hospitilized elderly patients [11].

2. Malnutrition in the elderly

The phenomenon of malnutrition in the elderly is more complex than that in the young ones and is a determinant of developing morbidity and mortality. It has been associated with adverse health conditions such as prolonged hospital stay, reduced quality of life, delays in wound healing, infection, and decreased functional capacity in these individuals. The prevalence of malnutrition was reported as 5–10% in the elderly living at home, as 30–60% in elderly residents of nursing homes, and as 35–65% in the elderly that have been hospitilized [12]. Considering that the daily energy requirement of people in this age group is 30 kcal/kg on average (in the absence of any stress situation under normal conditions), 50–60% of this energy should be planned to come from carbohydrates, 30% from fat, and 20% from proteins. While the daily protein requirement of a normal adult is 0.8–1.0 g/kg, the need is 1.0–1.2 g/kg per day under normal conditions, since muscle mass loss occurs in the elderly due to various reasons (sarcopenia) [13].

In cases of clinical diseases (such as infection, sepsis, cancer, etc.) that put the person in the acute catobolic process, the need for protein increases, and it can reach up to 1.5–2.0 g/kg per day. Vegetable proteins can be preferred as a protein source, but it is important to prefer animal proteins as they are limited in terms of both content and the presence of essential amino acids. Since most of the daily energy requirement is provided by carbohydrates, when its amount in the diet is reduced, it will cause fat and protein breakdown, which will lead to weight loss and sarcopenia. The omega-3 fatty acids in the dietary fat are important because of their anti-inflammatory character and positive effects on the cardiovascular system. On the other hand, it also has appetite-stimulating properties. Foods containing omega-3 fatty acids are fish, green vegetables, nuts, and walnuts. Adequate daily water consumption is also very important in old age. When this need is not met, it causes serious problems [13].

Dehydration and secondary medical emergencies to dehydration are responsible for a significant portion of hospitalizations in the elderly (e.g., acute renal failure, falls, arrhythmias, heart failure, electrolyte imbalance, etc.). The daily water requirement in the elderly is roughly 1 ml per kcal of daily energy requirement and is 30 ml per kg with another simple calculation. Another important nutrient is fiber (pulp). The first of the physiological changes that occur in the gastrointestinal system with aging is a decrease in movements. This problem can be partially solved by increasing the amount of fiber in the diet. On the other hand, dietary fiber plays an important role in blood sugar regulation. Therefore, the daily diet of the elderly should contain at least 25 g of fiber. 37–40% of the elderly cannot be fed at a level to meet the daily energy requirement, two out of three elderly people skip a meal, and this situation has been described as "anorexia of aging" in recent years [13]. In the old age, the mortality rate increases by 9–38% within 1–2.5 years following the onset of weight loss for any reason [14]. In addition to the decrease in oral food intake, daily growth hormone secretion decreases by 29–70% with age, which leads to sarcopenia [15]. In the frail elderly, different factors can occur at the same time and affect food intake by interacting with each other, and in the process of food intake and digestion, imbalances, weight loss, and loss of function may occur in the acute and chronic periods; in other words, malnutrition may occur. In **Table 1**, possible causes for inadequate food intake and malnutrition are listed under four subunits: somatic, psychological, functional, and social [7].

An increase in the incidence of depression, stool incontinence, loss of cognitive function, and physical dependence has been detected, especially in those with malnutrition [16]. There has been a significant increase in the incidence of other geriatric syndromes in the elderly with malnutrition. The risk of malnutrition was found to be associated with the levels of depression, hematocrit, fasting plasma glucose, albumin, erythrocyte sedimentation rate, instrumental activities of daily living, patient addiction, and bone mineral density [16, 17]. There has been a significant increase in the incidence of other geriatric syndromes in the elderly with malnutrition [16]. Although the effect of malnutrition on our country's economy is not fully known, it can be estimated that its negative effects are very high. It is known that such problems and costs will increase with the increase in the elderly group and chronic diseases in the aging world and in our country. The results of multicenter nutrition and health research conducted at the national level in the elderly show that there is an inadequacy in the consumption of energy, protein, vitamins A, B1 and B2, niacin and vitamin C, and minerals such as iron, calcium, and zinc, both at home and in the elderly living in nursing homes. Although the incidence of folate and vitamin B12 insufficiency in the elderly is not known in the whole population, it is known that insufficiency of these two vitamins in older ages is an important cause of cardiovascular diseases [7].

2.1 Prevalence

In a study, the malnutrition rate was found as 5.8% in the elderly living in the community, as 13.8% in those living in nursing homes, and as 38.7% in those hospitalized. There was a significant relationship between malnutrition and dementia and sarcopenia. In that study, mini-nutritional assessment (MNA) is recommended for the evaluation of the nutritional status of the geriatric age group [13]. In the ESPEN recommendations published in 2002, it is recommended that all individuals over the age of 65 should be screened routinely in terms of nutrition. Similar recommendations are included in all ESPEN guidelines published in the following years [17]. In the framework of the decision taken by the European Parliament in 2007, obesity and malnutrition were accepted as the most important public health problem, and the issue was included in the official political agenda of the European Union in 2008. The year 2009 has been declared the year of fight against malnutrition by ESPEN. Based on all these data, the nutritional status of elderly individuals living in the community and hospitalized in clinics should be screened, and a treatment plan should be developed by making detailed evaluations in risky individuals [2, 7].

Somatic state	Chronic diseases (eg: cancer, diabetes, chronic obstructive pulmonary disease, cardiovascular diseases) • Hospitalization • Operation • Acute illness • Pressure sores—Polypharmacy/side effects of drugs • Chewing and/or swallowing difficulties • Decreased sense of smell and taste • Gastrointestinal problems [nausea, vomiting, constipation, diarrhea]
Psychological state	Stress • Reaction to loss [e.g., after losing spouse, home, mobility] • Depressive complaints • Cognitive disorders/dementia
Functional status	• Limitation of mobility • Addiction in instrumental and basic activities of daily living
Socioeconomic status	Not having sufficient financial means to reach food • Being widowed • The state of living alone • Social isolation—Inability to adapt to the environment • Meals not available at the desired time • One-sided diet—Poor feeding environment (ambience, lack of companions)

Table 1.
Causes of inadequate food intake in the elderly.

2.2 Effect of malnutrition on body functions

Hunger has important effects on the function and structure of organs. Loss rates of various organs have been demonstrated in a study conducted on autopsy of patients who died from manure [18]. According to the findings of that study, the heart and liver lost about 30% of their weight, while the spleen, kidney, and pancreas were also affected. In that study, 32 healthy men who underwent partial fasting for 24 weeks each lost 25% of their baseline body weight. Fat mass decreased to 30% of baseline, and FFM to 82% of baseline. Clinical observations have shown that the loss in FFM is greatest in skeletal muscle. In response to stress, muscle proteins are both precursors of gluconeogenesis and amino acid precursors for protein synthesis required for immune response and repair. This muscle wasting may be one reason why debilitated people have a higher risk of developing complications during acute illness or after surgery [2, 7, 19].

2.2.1 Mental function

In adults, hunger causes anxiety and depression, which may be due to specific micro and macronutrient deficiencies. Several large-scale epidemiological studies have shown a relationship between diet quality and the frequency of cognitive impairment. Subclinical deficiencies of vitamins C, E, B12, B6, and folate, and changes in calcium, magnesium, and phosphate have been identified as nutritional-related risk factors for impaired brain functions [20].

2.2.2 Muscle function

Malnutrition causes a decrease in muscle strength and endurance. With a lack of food, muscle function decreases before any change in muscle mass occurs, then worsens as the amount of cells decreases. Conversely, through its effects on cell function, function improves by 10–20% in the first few days of refeeding. Then, over a period of weeks, the muscle mass is restored and gradually returns to normal. In addition to muscle wasting, inflammatory activity all reduces muscle strength, endurance, and mobility. Muscle strength is a combined measure of muscle mass and inflammatory activity and is therefore a useful risk factor for quality of life and ability to cope with trauma and disease. The hand-grip dynamometer, which measures voluntary muscle strength, is a useful clinical tool for nutritional assessment and has been found to be correlated with surgical outcomes and clinical improvement [6].

2.2.3 Cardiovascular function

Prolonged and severe malnutrition causes cardiac muscle wasting with decreased cardiac output, bradycardia, and hypotension. The reduction in heart volume, 40% of which is due to the reduction in heart muscle, is proportional to body weight loss. Decreased ventricular volume may explain the remaining 60%. In severely depleted patients, exercise tolerance is impaired and peripheral circulatory failure may also develop. Specific deficiencies such as vitamin B1 may lead to heart failure (wet beriberi), and mineral and electrolyte disturbances may lead to cardiac arrhythmias [21].

2.2.4 Renal functions

It has been reported that malnutrition causes significant changes in renal hemodynamics with a decrease in renal plasma flow and glomerular filtration rate, as well as a decrease in the capacity of concentrating urine and removing acid load. The capacity to remove excess water and salt load is also reduced, and the extravascular fluid volume makes up a larger-than-normal body part. Together with other malnutrition-related changes, these cause "hunger edema" [5].

2.2.5 Respiratory function

Protein loss of more than 20% affects the structure and function of respiratory muscles. This is accompanied by a decrease in diaphragmatic muscle mass, maximal voluntary ventilation, and respiratory muscle strength. Impaired neural respiratory power also affects ventilation. Exhausted individuals have impaired response to hypoxia and hypercapnia, altered respiratory pattern, and morphological changes in the pulmonary parenchyma. It is quite difficult to separate the patients from the ventilator. Bronchopneumonia is common in such patients, resulting in hypoventilation, inability to cough effectively, and impaired resistance to spreading microbes [5].

2.2.6 Gastrointestinal system

The most prominent effect of acute and chronic food starvation in the small intestine is a decrease in the absorption surface area. Impaired absorption of lipids, disaccharides, and glucose has been demonstrated in severely depleted patients. There is also a decrease in the production of gastric, pancreatic, and biliary secretions, which also contribute to malabsorption. As a result of these changes, severely malnourished patients often suffer diarrhea that is added to the malnutrition, and a vicious cycle begins. Changes in the bacterial flora or significant intestinal infections add to malabsorption and diarrhea. All gastrointestinal changes associated with malnutrition lead to inflammation and impaired intestinal barrier function. In chronic cases, this leads to liver steatosis or worse, steatohepatitis [5].

2.2.7 Thermoregulation

Severe weight loss impairs the thermogenic response to fasting and cold, and fasting for more than 48 hours reduces vasoconstrictive responses. These changes predispose to mild hypothermia with important clinical consequences. A decrease of only 1–2°C in core body temperature leads to impaired cognitive functions, incoordination, confusion, and muscle weakness, which tends to decline, especially in the elderly. In cases of severe famine, the fever response is lost, and there may be no fever even in the presence of life-threatening infection. Loss of thermoregulation returns after refeeding [5].

2.2.8 Immune system

Malnutrition itself affects nearly all immune response systems, but particularly impairs cellular immunity and resistance to infection. As a result of decreased immunity, susceptibility to infections increases, and the ability to cope with trauma and infection decreases. Annually, people with a BMI below 18.5 kg/m^2 tend to be sick more days than most people with a BMI above 18.5 kg/m^2 [21].

2.2.9 Wound healing

Malnutrition, and especially in the last period, low food intake, delays wound healing in surgical patients. Low body mass index, low body weight, and decreased food intake have been shown as independent risk factors for the development of pressure ulcers. An adequate diet improves wound healing in a week. There is evidence that nutritional support reduces the incidence of pressure ulcer development and that patients receiving high protein supplementation tend to have better healing of pressure ulcers [22].

2.2.10 Quality of life

Good nutrition improves quality of life, food itself not only provides sensory and psychological satisfaction, but also depends on it for mental and physical well-being. The consequences of malnutrition include progressive physical, mental, and social disability, and an increased propensity for diseases and their worsening [5].

2.3 Diagnosis in malnutrition

Before making a diagnosis of malnutrition, risk groups should be screened. Screening tests are used for this. With these tests, people to be investigated for the diagnosis of manutrition are determined [5].

2.3.1 Screening

A good screening method should be simple to implement quickly and easily by practitioners, as well as have criteria such as predictive validity, content validity, and reliability, and should provide a correct orientation for diagnosis. For this purpose, many malnutrition screening methods have been developed recently. These methods include questions about weight, recent weight loss, if any, and food intake. At the same time, weight, height, net measurements, and BMI calculation are used in these methods [23, 24].

2.3.2 Screening methods

Malnutrition Screening Tool (MST) and Short Nutritional Assessment Questionnaire (SNAQ) can be given as examples of short, easily applicable screening methods that can be used in malnutrition screening. Some screening methods, on the other hand, are considered as an evaluation method, not a screening method, since they include inquiries such as clinical status, physical examination, disease severity, and food amount. Subjective Global Assessment (SGA) is one of these assessment methods. SGA has been used as a screening method for more than 20 years and is used as a reference in the development of new methods. Nutritional Risk Screening (NRS2002) supported by ESPEN and Malnutrition Universal Screening Tool (MUST) developed by British Association for Parenteral and Enteral Nutrition (BAPEN) are other screening methods widely used in Europe. Simple training is needed for the use of SGA, NRS-2002, and MUST [23, 24]. Some of these screening methods are more suitable for different patient categories. For example, NRS-2002 or MUST, SNAQ, or MST is more suitable methods for hospitalized adult patients. For community surveys, it has proven its MUST value. For the elderly in the hospital or community, MNA and its short form MNA-SF are suitable [25]. The patients whose malnutrition will be evaluated with screening tests are determined and the evaluation phase is started.

2.4 Evaluation of malnutrition

Nutritional evaluation is a more detailed and time-consuming evaluation process by dietitians, nurses, or doctors experienced in clinical nutrition of patients who are determined to be in the risk group in nutritional screening. Thus, an approach plan can be created that includes continuous monitoring and an appropriate treatment approach.

Malnutrition assessment should include the following principles:

- Nutrient balance measurement
- Body composition measurement
- Inflammatory activity measurement

- Body functions measurement
- Laboratory tests [23–25].

2.4.1 Nutrient balance measurement

All potential factors that may cause malnutrition should be identified, and the course of the patient's condition should be predicted. Weight loss, food intake, appetite status, fluid balance, gastrointestinal symptoms, fever, various food losses, medical and drug use history should be evaluated. Detailed and accurate information about food intake is critical for the assessment of nutritional status. A dietary history should include qualitative as well as quantitative aspects to assess energy, protein, and micronutrient intake, as well as to estimate whether there is improvement or deterioration in the patient's nutritional status by comparison with predicted requirements. Making a good quality assessment is time-consuming and requires the specific experience of trained personnel. Evaluation of the diet in the last 24 hours reveals the current situation, while questioning the dietary history gives an idea for longer periods. Food diaries are indicative of individual intake, but to be fully reliable the questioner must ask additional questions. This type of query is only meaningful when used for the target population. Fluid balance is an intrinsic part of nutritional assessment. Physical examination should be performed to detect dehydration and edema. For this purpose, fluid balance records should be kept and blood creatinine, urea, and electrolyte levels should be measured when clinical indications are available [5]. Although it is not very common in daily practice, the energy requirement can best be determined by indirect calorimetry. There are many equations for estimating the energy requirement, but most of them deviate significantly from the actual values determined by indirect calorimetry. Isolated deficiencies can be determined by laboratory tests. Examples of these are minerals (i.e., K, Ca, Mg, Zn, Fe), vitamins, and trace elements [26].

2.4.2 Body composition measurement

Body weight, height, and calculated BMI are key measurements that should always be determined. Other anthropometric measurements, although easy, have not been popular. Anthropometric techniques measuring body compartments (fat free mass [FFM], fat mass [FM], skinfold thickness [TSFT], mid-arm muscle circumference [MAMC]) have been used in many studies. They may be useful in conditions where weight is difficult (i.e., elderly people with a fractured femur) [26].

2.4.3 Inflammatory activity measurement

The status of malnutrition should be determined not only by anamnesis, physical examination, and bedside measurements such as fever, pulse, and blood pressure, but also by laboratory tests such as hemoglobin, complete blood count, serum albumin, and c-reactive protein, which show the severity of inflammation [22].

2.4.4 Body functions measurement

Physical dysfunction related to malnutrition can be measured at the bedside with simple measurements that can identify the initial condition and allow monitoring. Evaluation of skeletal muscle function is important as it is sensitive to changes in muscle mass and food intake. Improvements in muscle strength occur within 2–3 days of starting nutritional support, but are not accompanied by an increase in muscle mass. Conversely, with total starvation, decreases in muscle strength begin within a few days. Muscle functions can be evaluated qualitatively by anamnesis and examination, as well as reductions in daily living activities and strength of handshake. The simplest quantitative measurement is with a handheld dynamometer, which correlates very well with clinical outcomes in surgical patients. Changes in respiratory muscle strength can be assessed by serial FEV1 measurements, bearing in mind that of course this also reflects changes in airway resistance. Evaluation of cognitive functions is not common. Malnourished patients exhibit a reversible deterioration in cognitive functions and mood. Using a valid mental scoring technique such as profile of mood states (POMS) or Mini-Mental State Examination (MMSE), mood swings should be scored and changes with treatment should be recorded [27, 28].

2.4.5 Methods used in nutritional evaluation

2.4.5.1 Anthropometric measurement

This measurement shows anatomical changes related to changes in body malnutrition status.

2.4.5.2 Body weight measurement

Changes in body weight in the short term reflect fluid balance and are the most important measure of fluid balance. Long-term changes in body weight, on the other hand, may reflect net changes in true tissue mass, but do not provide information about compositional changes. Involuntary weight loss in the last 3–6 months is considered mild if it is less than 5%, and if it is more than 10–15%, it is considered as an indicator of a severe nutritional change. Even if significant body weight has been lost in the past year, this does not reflect malnutrition if the lost body weight has recently been regained. However, if the loss of body weight continues, the clinician should investigate the reasons for this. Measured body weight is an important variable in calculating metabolic rate, nutritional requirement, and drug doses. Compared with indirect calorimetry, it is more accurate to use ideal body weight for calculations in overweight or underweight individuals, even though the metabolic rate estimates obtained with the equations may show deviations of up to 28%. Weight divided by ideal weight gives "percent of ideal body weight." Reference tables are available for individuals of the same age and sex, giving the ideal weight specific to the North American population. Ideal weights are determined by American health insurance companies on the basis of minimum health expenses [5, 18].

2.4.5.3 Body mass index

It is another measure to evaluate malnutrition. It is expressed according to the formula below. Although it has a narrow normal range, it offers a wide range that allows comparison in both sexes and age groups.

$$\text{BMI} = \text{Weight (kg)}/(\text{Height X Height})\ (\text{mxm})$$

The result obtained is interpreted according to the following values:

- 30< obese
- 25–30 overweight
- 20–25 normal
- 18–20 possible malnutrition
- 23.5< indicates adequate nutritional status.

If the BMI is less than 12 in men and 10 in women, survival is rare. If the body mass index is below 20, mortality increases. As a result of osteoporosis in the elderly, this range is increased with a decrease in height, and a BMI lower than 22 indicates malnutrition. If the patient has recently complained of involuntary weight loss, this is associated with malnutrition, even if the BMI is obese or even within the normal range. Estimated height can be calculated by adjusting age and knee height measurements according to gender in patients, elderly and frail people, or in cases of scoliosis or kyphosis and when height measurement cannot be performed [5].

2.4.5.4 Mid-upper arm circumference (MUAC), triceps skinfold thickness (TSF)

Mid-upper arm circumference (MUAC) is measured from the midpoint of the acromion and olecranon prominence using a tape measure. This measurement process is very easy and the margin of error is very small. It is a useful measurement method that replaces weight measurement in situations where weight measurement is impossible. Low measurement values correlate well with mortality, morbidity, and response to nutritional support. It has been determined that MUAC is a better predictor of mortality than BMI in the elderly population. The value obtained as a result of the upper middle arm circumference measurement; it reflects the sum of tissue, bone, muscle, fluid, and fat mass. However, useful correlations of muscle and fat mass can be obtained when triceps is used together with the measurement of skinfold thickness [5].

2.4.6 Advanced functional tests

2.4.6.1 Direct muscle stimulation

It provides the drawing of force frequency curves as a result of direct measurement of contraction, relaxation, and force by electrical stimulation of the adductor pollicis muscle. It can detect early changes with starvation and refeeding [5].

2.4.6.2 Respiratory function

Besides measuring airway resistance, FEV1 reflects the strength of respiratory muscles. Expiratory and inspiratory force against resistance can also be measured. Hill demonstrated a strong correlation between respiratory function and total body proteins after a rapid loss of 20% in body proteins [5].

2.4.6.3 Immune function

Severe protein energy malnutrition results in impairment of all factors such as cellular immunity, phagocyte function, complement system, secretory IgA, antibody concentrations, and cytokine production. Deficiency of some nutrients (e.g., zinc, selenium, iron, and vitamins A, C, E, B6) also alters the immune response. In the presence of malnutrition, leukocyte functions, antibody secretion, and complement levels may also be impaired [7, 29].

2.4.7 Laboratory tests

2.4.7.1 Serum albumin level

Although a good indicator of surgical risk and a good reflection of disease severity, it does not reflect malnutrition, contrary to popular belief. Delays in normalization of serum albumin during acute illness may be affected by energy and protein intake. Serum albumin is mainly affected by distribution and dilution. This is due to the increased rate of albumin escape from the circulation in relation to the cytokine response to injury and the dilution resulting from the increase in extravascular volume. Albumin has a long metabolic half-life of 18 days, the metabolic effects on its concentration take time to appear. In fact, the normal outflow of albumin from the circulation and its return through the lymphatics is approximately 10 times the synthesis rate [5, 7].

Proteins with shorter half-lives are affected by distribution and dilution, such as transthyretin (2 days) and transferrin (7 days) albumin. Transthyretin more accurately reflects recent food intake, but is not a good indicator of nutritional status. Therefore, these parameters are rarely included in a complete nutritional assessment [5, 7].

2.4.7.2 Other tests

Liver enzyme tests, creatinine, urea and electrolyte levels, calcium, phosphate, and magnesium levels should be measured routinely and recorded regularly. It is useful to know the zinc, selenium, and iron levels in the diagnosis of gastrointestinal diseases. C-reactive protein is useful for assessing acute inflammatory activity, but is not reliable for chronic inflammation or recovery from acute inflammation [5, 7].

2.4.7.3 Creatinine

Urinary excretion of creatinine reflects muscle mass. Urinary excretion of creatinine is high in weight lifters with a large muscle mass and low in malnourished patients. The creatinine excretion in 24 hours is used to calculate the creatinine height index (CHI).

$$\text{CHI}(\%) = 24 - \text{hour persistence creatinine x } 100$$

This formula is used to reflect muscle mass. If the deficit in muscle mass is 5–15%, it is mild, if it is between 15 and 30%, it is moderate, and if it is more than 30%, it indicates a severe nutritional deterioration.

Nitrogen balance is one of the most frequently used research methods in clinical practice, which always overestimates the intake and underestimates the losses from urine, faeces, and wounds. For total nitrogen, the Kjeldahl technique is better than inferring from urine urea. Under normal conditions, urea contains 80% of urinary nitrogen, but this ratio varies with malnutrition and disease. Nevertheless, large changes in urinary urea excretion are useful in demonstrating changes in net protein catabolism and are a simple method to apply in intensive care. Decreased protein turnover with fasting is characterized by low serum urea concentration if patients are well hydrated [5, 7].

2.5 Saving data

It is absolutely essential that the data obtained by monitoring at the beginning and maintenance of nutritional support be recorded in a digital environment or on paper and be easily accessible for control when necessary. Thus, absolute values or trends can be easily monitored and decisions can be made quickly when necessary. In order to better reflect the clinical situation, the correlation or combination of various parameters paves the way for more effective predictions [5].

2.6 Evaluation of results and diagnosis

Today, there are many tools available for screening and diagnosing malnutrition. To prevent misuse, it is important to know how they were developed and for which specific patient population and department of care they were evaluated. The methods used in screening and diagnosis are important in recognizing the disease with malnutrition, finding the underlying causes of malnutrition, and evaluating the consequences of malnutrition [30, 31]. Screening instruments are short, time-consuming, easy for the patient, and often do not require the expertise of the personnel performing these tasks. Screening tools often indicate only malnutrition. For patients at risk, it is necessary to learn more about the cause, severity, and pattern of malnutrition (such as protein-energy malnutrition, vitamins, and minerals) [32, 33].

The tests used in the diagnosis of malnutrition give an opinion about the severity and type of malnutrition and the underlying factors. Diagnostic tools are more complex in shape than screening tools, take more time, and require more experienced personnel. The results of the laboratory and/or clinical research may form part of this evaluation [33, 34].

The most commonly used assessment tool specifically for malnutrition in the elderly is the Mini Nutritional Assessment test (MNA) [1, 32]. Subjective global assessment is another test that is accepted as a basis by the social security institution and is frequently and widely used in the screening and diagnosis of malnutrition. Comprehensive geriatric assessment is a method that ensures that many problems of an elderly person are evaluated and followed up as effectively as possible. Comprehensive Geriatric Evaluation is put into practice in order to obtain a full-fledged result in terms of the geriatric patient's condition. Thus, the patient is evaluated in terms of somatic, psychological, social, and functional aspects, and an integral treatment plan is created for the patient to manage himself and improve his quality of life [35, 36]. Malnutrition is a geriatric syndrome and must be included in a comprehensive geriatric evaluation. Comprehensive geriatric evaluation also evaluates the relationship of malnutrition with other somatic, psychological, social, and functional conditions. MNA is recommended in the evaluation of malnutrition in the elderly. MNA is a valid method for detecting malnutrition in clinical as well as outpatients. The MNA is also a valid tool for evaluating the results of nutritional support treatments. MNA is accepted as a valid measurement tool for detecting malnutrition in geriatric patients, as well as a valid tool for predetermining the risk of malnutrition. ESPEN recommends MNA as an examination tool for the elderly [32, 37]. It is a tool that must be used in SGA and has practical benefits.

2.6.1 MNA form

The MNA begins with six screening questions (questions A-F1/F2), which are MNA-Short form (MNA-SF) with a maximum of 14 points. These questions relate to the patient's food intake, weight loss, mobility, psychological stress or acute illness, depression or memory problems, and determination of BMI. If BMI cannot be measured, it has been proven that the use of calf circumference may be appropriate [38]. If a score of less than 12 points is obtained as a result of this questioning, it is recommended to continue with the other questions (questions G-S). These questions are related to residence status, medication use, presence of pressure sores or skin inflammation, eating meals and protein and fluid intake, patient's own opinion according to nutrition and health status, and some extra anthropometric measurements [32, 37]. This will be the final MNA-score: <17 means malnutrition, 17–23.5 means malnutrition risk, and >23.5 indicates adequate nutritional status. Fill in the ”Examination” section of the form. If the total score is 11 or less, proceed to the questions under the “Research” section to determine the score for the Nutritional Malnutrition Indicator. The administration of MNA-SF takes less than 5 minutes, while the administration of full MNA requires 10–15 minutes. SGA is also a very useful and frequently applied test. In the current situation, it is frequently used in diagnosis. However, it includes subjectivity in practice. SGA is one of the easy and practical methods in determining the nutritional status of individuals. It is one of the tests required to be specified when a report is issued for the reimbursement of malnutrition products. It includes evaluation criteria such as the patient's history (weight loss, change in food intake, gastrointestinal symptoms, and functional status), physical tests (muscle mass, subcutaneous fat, sacral and foot edema, ascites). Does not include SGA lab data. It is thought that adding this information to the test will not affect the performance of the test in detecting malnutrition. It has been reported that the weight index is the main factor affecting the subjective evaluation. The feature of this screening test is that it can be used in the elderly population. In long-term care, it has been found to be a useful assessment tool in identifying the elderly at high risk for complications associated with changes in nutritional levels (major infections, pressure sores, and mortality) [38–41].

2.6.2 Tests used for inpatients

Malnutrition Universal Screening Tool (MUST) [20], Short Nutritional Assessment Questionnaire (SNAQ) [42], Nutritional Risk Screening (NRS2002) [19]

2.6.3 Tests used for outpatients

Mini Nutritional Assessment Test Short Form (MNA-SF) [25, 32], Subjective Global Assessment (SGA).

In addition, using anthropometric measurements other than BMI will provide additional contributions in detecting malnutrition and the underlying causes of malnutrition [43].

2.6.4 Practical meaning

Comprehensive geriatric assessment consists of the following sections:

- Medical history
- Family interview
- Functional anamnesis
- Social history
- Physical examination
- Clinical measuring instruments
- Laboratory research

History is a standard part of Comprehensive Geriatric Evaluation. In anamnesis; decreased appetite, decreased sense of smell or taste, weight loss, nausea, vomiting, diarrhea, chewing and swallowing problems should be questioned. However, indicators of malnutrition can be found in all parts of the comprehensive geriatric assessment. Being in need of care in the functional history is a risk factor for malnutrition. In the social anamnesis, living alone or not having a caregiver who takes care of the needs of the elderly is known as a risk for malnutrition. In the physical examination, information about the nutritional status can be obtained by determining the clinical evaluation of the patient's nutrition and hydration status (weak, cachectic, dry axilla and mouth), height, weight, and BMI. By looking at muscle mass (atrophy, sarcopenia) and muscle strength, information about the symptoms and possible consequences of malnutrition can be obtained. Based on the results of the comprehensive geriatric assessment and MNA, the patient's problem list should include data on malnutrition problem or risk in malnutrition. At the same time, the most important factors that reveal the problem of malnutrition from both results will be seen. These factors may be, for example, reduced self-care and malnutrition due to moderate to severe dementia. In such a case, a nutrition plan should be drawn and followed during the patient's hospitalization or discharge. The treatment plan is aimed at adequate food intake on the one hand and treating the factors that cause it, on the other. For example, when such a patient goes home after being discharged from the hospital, he should be kept under control while taking his meals, and the meals given to him should be enriched with energy and nutrients, and he should be weighed and checked on a weekly basis during the home care period. However, many of the elderly patients do not know exactly how much weight loss occurs, it is not always possible to measure weight in polyclinic conditions, or it is not possible to measure the weight of bedridden patients. In such cases, the use of other acceptable anthropometric measurements such as calf measurement, skinfold thickness measurement instead of weight and body mass index will facilitate the work of doctors, patients, and patient relatives, especially in order to provide easier nutrition products for patients. It would be appropriate to define these measurements in the national health network system and include them in the scope of reimbursement [30, 43].

2.7 Treatment

Nutritional support treatment should be planned for patients with malnutrition or risk of malnutrition as a result of screening and evaluation.

This can be done in two ways:

- First of all, in those who can take oral food, a diet is arranged in line with the daily calorie needs by consulting the diet unit of the clinic. Considering the patient's preferences is the determinant of success; but unfortunately, since a rich diet kitchen is not possible in our hospitals today, adequate support cannot be provided in this way.

- The second way is supportive treatment with enteral and/or parenteral nutrition products.

Enteral nutrition is essential in this treatment modality, but this is not always sufficient or possible, so it is sometimes supplemented with parenteral nutrition therapy. Enteral nutrition routes are oral enteral, nasoenteral, and enterocutaneous routes. Nasogastric or nasointestinal feeding tube can be used for the nasoenteral route. Silicone or polyurethane tubes should be preferred. Enterocutaneous routes are percutaneous endoscopic gastrostomy (PEG) and percutaneous endoscopic jejunostomy (PEJ). Sometimes the jejunum can be reached through a tube extended from the PEG (PEG-J). In the geriatric part of the enteral nutrition guide published by ESPEN in 2006, it is emphasized that oral nutritional support should be provided as much as possible in the frail elderly during the selection of the nutrition route. In the presence of neurological dysphagia, it is recommended to choose one of the enteral nutrition routes, choose products with fiber content, and give products with high protein content in the presence of pressure sores. It was emphasized that oral or tube feeding therapy should be given in patients with early and moderate dementia, and tube feeding should not be preferred in patients with advanced dementia. It is also recommended not to apply tube feeding in terminal stage cancer patients. PEG is recommended for patients who require long-term tube feeding (>4 weeks) [30]. After choosing the nutritional route, the daily energy requirement should be calculated, and then the amount of support to be given daily should be calculated by considering the oral food intake. The daily energy requirement can be found by adding the basal energy requirement, the activity factor, and the stress factor. We use practical formulas to calculate basal energy requirement. The most accurate way is to measure with an indirect calorimeter. The use of formulas saves time and is cost-effective and must be within ±10% standard deviation from actual measurements. The most commonly used formula is the Harris-Benedict formula. Calculation is made using weight, height, and age. After the basal energy requirement is found, the stress factor is determined by looking at the clinical disease and clinical findings and added to the basal energy requirement [44].

After calculating the daily energy requirement, two ways can be used to calculate the current deficit:

- In the first, the patient is advised to list what they eat and the daily calorie intake is calculated from this list.

- The other way is to question the ratio of the amount of food consumed today compared with the past. It is asked whether it consumes half of it compared with before, and then it is not satisfied with it, and it is questioned in more detail whether it is less or more. A ratio that can be obtained from here will approximately show the amount of energy it receives over the daily energy requirement. After calculating the daily calorie deficit, daily protein needs and water needs should be calculated. In addition, in the presence of special conditions (diabetes, cancer, sepsis, chronic kidney failure, congestive heart failure, etc.), appropriate nutrient ratios should be determined. Fibers gain importance in the maintenance of gastrointestinal system motility in elderly patients, and fiber should be added to the diet. During enteral nutrition, it is important to choose the appropriate product according to the clinical situation. Under normal conditions, standard products with different flavors are preferred, and special products are used in unusual cases. Standard products usually contain 1 kcal per 1 ml. They have moderate osmolarity and good tolerability. Nutrient ratios are at the levels of carbohydrate 50%, fat 30%, and protein 20%. They contain essential nutrients as well as vitamins and trace elements. Diabetic products contain less carbohydrate and molecules with lower glycemic indexes such as fructose, isomaltose, and maltodextrin are chosen. High-energy products are preferred in patients who need fluid restriction (1 ml=1.5–2 kcal). For this reason, their osmolarity is also high, tolerability is more difficult. Protein content is higher in protein-rich products. There are various soluble or insoluble fibers in fiber-rich products. While these fibers contribute to motility on the one hand, they also create a prebiotic effect. When tolerance cannot be achieved in others, products with low osmolarity may be preferred. Their osmolarity varies between 240 and 300 mosm/l. There are products developed for use in cancer cachexia and inflammatory diseases and containing various immunonutrition products (glutamine, arginine, RNA, eicosapentaenoic acid (EPA)). There are data showing that they are especially beneficial in cancer cachexia, they are appetizing. While glutamine stands out in terms of gastrointestinal system tolerability, antioxidant properties and anti-inflammatory contribution on the immune system, arginine in wound healing and EPA in increasing appetite gain importance. In various diseases in which intestinal absorption is affected, products containing semi-elementary and elementary molecules can be preferred. For example, medium-chain fatty acids (MCTs) are absorbed from the intestine, while they do not need lipoprotein lipase and are absorbed directly from the mucosa without the need for micelles and reach the liver by mixing directly with the portal system. It can be especially useful in conditions such as short bowel syndrome, inflammatory bowel disease, and cholestasis. Recently, support products consisting of combinations of arginine, glutamine, leucine, and its 52 metabolite hydroxy methyl butyrate (HMB), which are known to be effective in the healing of pressure sores, have taken their place in the market. In particular, HMB not only triggers collagen synthesis and protein synthesis, but also stops protein degradation, and is 200 times more potent than leucine, of which it is a metabolite. After calculating the daily energy deficit and choosing the appropriate enteral nutrition product, the first thing to do is how quickly this product should be given or how long it takes to reach the target volume. Because reaching the target quickly may cause complications such as tolerance disorders, vomiting, diarrhea, and aspiration. Generally, the recommended target amount is to be reached in 7–10 days. The preference of oral enteral products in low-volume boxes is positive in terms of patient compliance. Aroma differences arise between societies. While fruity flavors are preferred more in Turkish society, vanilla and coffee can be tolerated better in Western societies. Products produced for tube support therapy should not be given orally. Nausea, vomiting, and diarrhea are the most common symptoms during treatment. For nausea and vomiting, treatment should not be stopped immediately, products that accelerate gastric emptying time and increase intestinal motility can be used. On the other hand, the amount of product may be reduced for a while or a different product may be tried. When diarrhea occurs, first of all, the presence of infection should be investigated by stool analysis. In some cases, treatments that suppress bowel movements can be given (such as loperamide in short bowel syndrome). Since the risk of aspiration will increase in the elderly and those with neurological diseases, gastric residual determination should be made, especially in tube feds. In the presence of 200 cc or more residue, the amount or speed of outgoing product should be reduced, or the product should be changed in the same way or supportive treatments should be added. During bolus applications during tube feeding, 25–50 cc of water should be given in front of and behind the product, and during infusion therapy, the outgoing product should be stopped at regular intervals and water should be given again. The same is true with PEG. In patients fed from the jejunum, hypo-osmolar products or water should not be given directly. Bolus administration should not be done. Only infusion therapy can be given. In all cases, the patient's head should be kept at a height of 30–400 meters. In cases where enteral nutrition is not possible or insufficient, parenteral therapy should be applied. There are two types; peripherally administered and centrally administered. The main difference between the products applied in both ways is the calories and fat they contain in unit volume. While there is 0.6–0.7 kcal in ml of products administered centrally, there is 1 kcal in ml of products administered via central route. Fats are molecules suitable for central administration. They are found in peripherally applied products at low rates. The standard oil used in parenteral products is soybean oil. Over time, olive-oil-based products, mixtures containing medium-chain fatty acids, and mixtures containing fish oil have been introduced to the market. Mixtures containing fish oil stand out with their high EPA content and their anti-inflammatory effects are known. Again, while an anti-inflammatory effect is observed in products containing olive oil, it has been reported in some articles that it can prevent fatty liver [44].

3. Cancer patients and malnutrition

Cancer usually occurs with advanced age. One of the most important reasons for weight loss in cancer patients is a decrease in food intake. Many factors cause this: Loss of appetite (tumor burden, treatment, depression), early satiety (gastrointestinal tract), other GI symptoms (nausea, vomiting), odynophagia (mocositis, fungal/viral esophagitis), dry mouth, dysphagia, chewing difficulty in reaching food as a result of a decrease in daily life activities, pain, and deterioration in quality of life. Poor oral hygiene, loss of teeth, space-occupying lesion, especially in tumors related to the gastrointestinal system, and due to the treatment that occurs or is used in the course of the disease (radiotherapy acute/chronic effect, chemotherapy-mucositis) loss of appetite can be seen as a result of side effects [44]. It causes some changes in carbohydrate, lipid, and protein metabolism. With the decrease in insulin sensitivity, impaired glucose tolerance develops, gluconeogenesis increases, and serum lactate level rises. Lipolysis increases and serum triglyceride levels increase and lipoprotein lipase activity may decrease. Negative nitrogen balance occurs as a result of excessive protein degradation. Proteolysis triggering factor and lipid mobilizing factor released by tumor cells cause excessive muscle destruction and lipolysis in the hypercatabolic process, and cytokines (TNF-alpha, IL-1, IL-6) oversynthesized by the body contribute to this [45]. 54 A correlation was found between IL-6 level and disease stage, acute phase response, and malnutrition status in patients with lung cancer [46]. A relationship was found between TNF- alpha, reduced oxygen products, reduced glutathione and vitamin E levels, and the development of anorexia-cachexia syndrome [47]. Circulating TNF levels were found to be higher, and serum albumin and IGF-1 levels were found to be lower in those with weight loss of >10% [48]. A relationship was found between anorexia-cachexia syndrome and parathormone-related peptide (PTHrP) levels, and it was understood that weight loss stopped and weight gain occurred when PTHrP was neutralized [49]. The ESPEN guideline states that "the nutritional status of cancer patients should be evaluated at frequent intervals and supportive treatment should be started early when deficiency is detected." There is no routine enteral nutritional support during chemotherapy and/or radiotherapy. Enteral nutrition should be started to make up the difference between the need and the calories taken from the diet, and 1.2–2.0 g/kg/day protein support should be provided during the treatment. It has been stated that there is no clear data that standard products can be given, immunonutrition products and antioxidant vitamins increase survival. In cases where enteral nutrition is not possible or insufficient, parenteral nutrition should be given [50].

4. Neurological diseases and malnutrition

Neurological diseases known to cause malnutrition include Alzheimer's disease, Parkinson's disease, myastania gravis, cerebrovascular accident, multiple sclerosis, and amyotrophic lateral sclerosis. Severe dysphagia may occur in the course of these diseases. The most important causes of malnutrition developing in the course of neurological diseases are depression, impaired self-care, difficulty in swallowing, and drugs. The result is muscle atrophy (extremity/respiratory), pressure sores, falls, osteoporosis, infection risk, and reduced survival. In the presence of cerebrovascular accident, malnutrition is diagnosed in 15% of patients at the time of admission, 22–35% in the second week, and in 50% of the patients during follow-up. In the presence of swallowing dysfunction, the risk of food aspiration increases and may result in death. It may be undesirable to give oral food before the first 48 hours of consciousness change. In a study comparing nasogastric catheter vs. PEG application in patients with dysphagia as a result of acute stroke, mortality rates increased nearly five times in those fed with nasogastric feding tube [51]. Before the tube is inserted, the patient should be evaluated in detail and the indication for long-term supportive treatment should be discussed. In this case, 55 PEG (percutaneous endoscopic gastrostomy) should be inserted instead of the tube. In theory, tube enteral nutrition should be used for a maximum of 6 weeks, and PEG should be preferred in cases exceeding this. On the other hand, malnutrition causes pressure ulcer development. In the ESPEN guideline, enteral nutrition is recommended for those with severe neurological dysphagia, oral nutritional support therapy, or tube feeding is recommended for patients with early-middle stage dementia, and tube feeding is not recommended for advanced dementia. Supportive therapy with high protein content regresses pressure sores. It is stated that PEG should be inserted instead of long-term tube feeding [52].

5. What else should we pay attention in malnutrition?

Efficacy should be considered during enteral or parenteral nutrition therapy. Apart from the improvement in general condition, weight gain, increase in serum proteins, and decrease in acute phase response are good indicators of treatment success. Close monitoring of potential side effects is important for treatment success. Especially in cachectic patients who have lost weight for a long time, rapid supportive treatment may cause serious metabolic complications. "Re-feeding syndrome" in which one or more of the conditions such as severe electrolyte imbalances, osmolarity changes, arrhythmias, overload, dehydration, acute kidney failure, sudden death, hyperglycemia, hypoglycemia can be seen together can be fatal. The most important way to prevent this is to reach the target calorie requirement slowly, especially in cachectic patients, this time can be much longer. "Re-feeding syndrome" is more common in such patients, especially during parenteral nutrition. In the follow-up, daily blood glucose monitoring, 2–3 times a week electrolyte, Blood Urea Nitrogen, creatinine monitoring (especially potassium, phosphorus and magnesium) are recommended. Trace element and vitamin support should not be forgotten during parenteral therapy. Thiamine deficiency is common in prolonged fasting. It can cause serious neurological disorders (i.e., Beri-beri) [44].

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Chapter 10

Perspective Chapter: Malnutrition and Air Pollution in Latin America – Impact of Two Stressors on Children's Health

Melisa Kurtz, Christian Lezon, Patricia Boyer and Deborah Tasat

Abstract

Nowadays, the evolution of the concept of nutrition has acquired a notion of three concurrent dimensions. Nutrition was considered an exclusively biological process while now, it comprises social and ecological aspects. Inadequate nutrition and air pollution are two major nongenetic environmental factors known to cause serious public health problems worldwide. Air pollution does not impact in the same way on the population at large, being particularly the children one of the most vulnerable subpopulations. Additionally, the nutritional status may modify the susceptibility to air pollution exposure and cause a wide range of acute and chronic cardio-respiratory diseases. Moreover, undernutrition is identified as a major health problem with devastating healthcare effects on the individual, social, and economic development. On a global scale, chronic undernourishment affects 144 million children younger than 5 years. However, the mechanism linking undernutrition and air pollution exposure still remains unclear. At present, only few epidemiological studies have been reported associating child malnutrition and air pollution. Therefore, a better understanding of the interactions between undernutrition and air pollution exposure is needed to guide action by individuals and governments.

Keywords: malnutrition, air pollution, children, health, public health

1. Introduction

From a holistic health perspective, the new concept of "nutrition" combines biological, social, and environmental dimensions as determinants of individual and collective health. The concept of "three-dimension nutrition" considers nutrition as a highly complex multidisciplinary approach to addressing health problems [1].

Thus, the concepts of nutritional adequacy and malnutrition are determined by three concurrent dimensions—(1) a biological dimension, which understands nutritional adequacy as an indispensable condition whereby the specific nutritional requirements of each stage of life are met; (2) a social dimension involving cultural factors, such as religion and education, and economic factors as determinants of eating habits; and (3) an environmental dimension, which comprises climate and geographic conditions associated with production, availability, and access to foods [1].

Inadequate nutrition and air pollution are two major nongenetic environmental factors that negatively affect body growth [2, 3]. In their 2003 report Framework for Cumulative Risk Assessment, the US Environmental Protection Agency (EPA) proposed a health risk analysis considering the combined effect of different types of stressors, including physical, chemical, biological, psychological, and social stressors, which together with the nutritional factor affect children's respiratory system—the main target of air pollution.

There are studies reporting an association between inadequate nutrition and exposure to air pollution, suggesting that the nutritional factor can act as a stressor compromising response to pollution-related stressors [4–7].

Indeed, environmental influences during prenatal and postnatal life can result in alterations in the normal patterns of epigenetic modification [2, 8]. An unbalanced diet can lead to hypomethylation, which in turn can cause genomic and chromosomal instability [2]. It is known that methyl groups are acquired through the diet and are donated to the DNA via the folate and methionine pathways. *In short, qualitative-quantitative diet variations can trigger metabolic and/or neuroendocrine dysfunctions that negatively affect body growth and development, mainly during critical periods of growth, with the ensuing risk of developing diverse diseases in adulthood.*

It is well documented that air pollution has devastating adverse effects on human health and is currently a significant problem that not only jeopardizes the health of thousands of millions of people [9] but also degrades the Earth's ecosystems, undermines the economic security of nations, and is recognized as one of the main causes of disease, disability, and premature death in the world.

Lave and Seskin were among the first to demonstrate a significant association between air pollution and child death due to environment-related respiratory diseases in their study across 117 U.S. metropolitan areas [10]. Although more recent studies conducted by our research group using a model that reproduces a condition of chronic human undernutrition showed that undernourished children are potentially a high-risk group [11], there is little information on the impact of the local and systemic effect of airborne particulate matter on undernourished children (**Table 1**).

Air pollution and undernutrition are considered a threat to world public health. Nevertheless, these risk factors can be decreased through governmental, educational, and political interventions aiming to prevent disease in the population at large, particularly in children—a vulnerable subpopulation.

Pub med search	No of publications
Infant AND [(malnutrition) OR (undernutrition)]	24,710
Infant AND [(air pollution) OR (particulate matter)]	6543
[(air pollution) OR (particulate matter)] AND [(malnutrition) OR (undernutrition)]	252
Infant AND [(air pollution) OR (particulate matter)] AND [(malnutrition) OR (undernutrition)]	71

Table 1.
Search syntax used and bibliography obtained from PubMed database.

The present bibliographical review study has been elaborated from a search of works published in the PubMed database. It may be accessed through several interfaces, including PubMed, Ovid Medline, and EBSCO Medline. The PubMed interface is available to anyone with an Internet connection; the Ovid and EBSCO interfaces require a subscription, either through a library or a personal account, so herein we chose to use the PubMed platform. PubMed® comprises more than 33 million citations for biomedical literature from MEDLINE, life science journals, and online books.

2. Malnutrition worldwide

2.1 Definition and classification

The World Health Organization (WHO) defines malnutrition as deficiencies, excesses, or imbalances between a person's intake of energy and/or nutrients and his/her body requirements for proper growth, maintenance, and function.

Malnutrition comprises three physiopathological conditions—(1) (a) wasting defined as low weight for normal height for age, (b) stunting, defined as low height for age whether (normal weight for height) or not (low weight for height), and (c) underweight, defined as low weight for age; (2) micronutrient deficiencies associated with inadequate intake of vitamins and/or minerals; and (3) overweight and obesity [12, 13].

Children with wasting are dangerously thin, and their immune system is weak [14]. Delayed growth impairs both physical growth and cognitive development and increases the risk of death due to common infectious diseases [15].

Insufficient intake of vitamins A and D, iron, calcium, and zinc can severely compromise the health and development of entire populations across the globe, especially children and pregnant women in low-income countries [16–19].

Worldwide, being overweight is associated with a higher intake of foods containing sugars and fats and lower physical activity levels. Its long-term consequences include cardiovascular disease, type 2 diabetes, and other metabolic diseases [20].

2.2 Nutritional insecurity

It is important to point out that the different forms of malnutrition can be aggravated by nutritional insecurity associated with poor health care, lack of safe drinking water and sanitation, poor housing conditions, and environmental crises, among other factors [21].

According to the 2021 State of Food Security and Nutrition in the World annual report prepared by the Food and Agriculture Organization of the United Nations, between 720 and 811 million people in the world faced hunger in 2020, 161 million more than in 2019 when considering the upper bound of the projected range. Of the total 768 million people facing undernutrition in the world, 282 million are in Africa and 60 million are in Latin America and the Caribbean. Thus, compared with 2019, 46 million more people in Africa, 57 million more in Asia, and almost 14 million more in Latin America and the Caribbean were affected by hunger in 2020.

Whereas the global prevalence of moderate and severe food insecurity has been increasing slowly since 2014, the estimated increase in 2020 was equal to that of the last 5 years combined. Almost one-third of the world population (2370 million people) did not have adequate access to food in 2020, nearly 320 million people more in only 1 year. The increase in food insecurity was more marked in Latin America (9%) and the Caribbean and Africa (5.4%) than in Asia (3.1%). No region in the world escaped this trend, including North America and Europe, where these figures increased for the first time since 2014. The high cost of healthy nutrition and the persistence of high poverty levels and low incomes have resulted in poor access to healthy foods for millions across the world.

The gender gap in the prevalence of moderate and severe food insecurity has increased at the global level and is 10% higher among women than men.

The COVID-19 pandemic has had a devastating impact on the global economy, triggering a recession unseen since the Second World War and affecting food security and the nutritional state of millions of people, including children. Although the impact of the COVID-19 pandemic cannot yet be determined precisely due to limitations in obtaining information, it is estimated that 22% (1492 million people) of children under the age of 5 years showed stunting, 6.7% (45.4 million) suffered wasting, and 5.7% (38.9 million) were overweight. The increase in food insecurity would seem to indicate that these figures continued to rise in 2021.

2.3 Undernutrition in Latin America

The prevalence of stunting and wasting among children under the age five years old is as follows: America: 5.6 million (2.93%), Africa: 70.2 million (36.8%), Europe: no data, Asia: 110.8 million (58%), and Australia/Oceania: 0.7 million (0.37%). Specifically, regarding the 5.6 million stunted and wasted children under 5 in America, 4.9 million (87.5%) live in Latin America and the Caribbean, and the remaining 0.7 million (12.5%) live in the US and Canada [22].

According to data on the prevalence of wasted and stunted children under the age of 5 in Latin America collected by the WHO from studies conducted in different periods, the prevalence of stunting among children under 5 was higher than 30% in Bolivia, Ecuador, Guatemala, Haiti, Honduras, and Peru, and less than 10% in Argentina, Cuba, and Costa Rica [23, 24]. The prevalence of stunting was lowest in Argentina (8.5%) and highest in Guatemala (54%). Wasting, a clear indication of severe undernutrition was highest in Haiti (20%), Honduras (13.1%), and Guatemala (18%). Prevalence was low in the remaining countries, ranging between 2.5 and 3.0% [23]. Significant surveys from 10 Latin American countries, namely Argentina, Bolivia, Brazil, Colombia, Chile, Ecuador, Guatemala, Mexico, Peru, and Uruguay conducted between 2005 and 2017 evidenced that children aged <5 years and women of reproductive age (11–49 years) were vulnerable population subgroups at high risk of all forms of malnutrition. Stunting and anemia were more prevalent among low-income and less-educated populations. Of note, Guatemala, Bolivia, and Peru had the highest stunting and anemia prevalence and the largest economic and social inequalities [24].

3. Air pollution worldwide

To a greater or lesser extent, we are all exposed to environmental pollution, and its impact on health can occur at all stages of life, from conception to old age.

Air pollution is a worldwide phenomenon and an inescapable part of modern life throughout the world. According to the World Health Organization [25], air pollution represents the largest environmental risk to global health. As shown by 2019 WHO report, 99% of the world population does not breathe clean air, and more than half the urban population is exposed to air pollution levels more than 2.5-fold higher than air quality standards. Ambient (outdoor) air pollution in both cities and rural areas was estimated to cause 4.2 million premature deaths per year. In addition to outdoor air pollution, indoor smoke is a serious health risk. In 2016, 3.8 million premature deaths were attributable to household air pollution, mainly due to the burning of biomass, kerosene fuels, and coal in inefficient stoves. Almost all of the burden was in low-middle-income countries.

Nevertheless, ambient pollution is a problem in a lot of high-income countries. Some European populations, such as those living in the United Kingdom, Germany, and France, are exposed to air pollution levels that exceed the health-based air quality guidelines set by the WHO [26]. It is estimated that even in cities where Particulate Matter (PM) concentration is within WHO air quality standards, exposure to anthropogenic PM decreases average life expectancy by 9 months [9].

At present, outdoor and indoor air pollution combined account for 7 million deaths worldwide [27].

In this context of rapid growth in population and urbanization and the challenges associated with technological and economic development and the consequent changes in land use, energy use, and transportation, careful urban planning and efficient city governance are paramount to ensure the provision of food, housing, and services while minimizing the impacts of urbanization and industry on anthropogenic and biogenic emissions that degrade air quality [28–30].

3.1 Definition and classification

Ambient air pollution is defined as the presence of substances in the atmospheric air at concentrations that can pose a risk to or damage the safety of people and the environment. Outdoor air pollution is a complex mixture of thousands of components, and from a health perspective, the important components of this mixture include airborne particulate matter (PM) and gaseous pollutants: Ozone (O_3), Nitrogen Oxides (NOx), Volatile Organic Compounds (VOCs), Carbon monoxide (CO), and Sulfur Oxides (SOx). In 2006, the Environmental Protection Agency (EPA) set the National Ambient Air Quality Standards (NAAQS) for six major pollutants, including particulate matter (PM10 and PM2.5) and ozone [31]. These air pollutants can originate from natural and anthropogenic sources. The main natural sources are volcanic eruptions, forest fires, and sand and dust storms and are usually extreme and sudden events. Pollutants generated by anthropogenic activity are released continuously and persistently into the atmosphere and are mainly generated by burning petroleum and biomass fuels [32]. Particulate matter (PM) is defined as the material suspended in the air in the form of solid particles or liquid droplets. PM is generated through the burning of fossil fuels (diesel, gas, methane, and coal) in vehicles, industry, and households [33]. The adverse health effects of PM inhalation are mainly associated with the size and physical-chemical characteristics of the particles [34]. Particles can be classified into three main groups according to their aerodynamic size—coarse particles (diameter ≥2.5 and <10 μm), fine particles (diameter ≥0.1 and <2.5 μm), and ultrafine particles (<0.1 μm). Resuspension of soil and road dust by wind and moving vehicles, tire wear, construction work, and industrial emissions are the main sources of coarse particles (PM_{10}). Fine particles ($PM_{2.5}$), composed of elemental carbon, transition metals, complex organic molecules, sulfate, and nitrate, result from combustion processes. Fine particles can travel great distances (> 100 km), which can potentially lead to high concentrations over a wide area.

In 2013, the International Agency for Research on Cancer (IARC) established that PM in outdoor air is carcinogenic to humans (Group 1) and causes lung cancer [35].

PM concentration is expressed as mg/m^3. Different organizations have established air quality guideline values set to protect human health. Nevertheless, values differ, and WHO limits are generally stricter than the comparable politically agreed EU standards. The recently revised WHO air quality standards [36] are below those established in 2005 [37].

Even when below recommended levels, PM and O_3 are linked to respiratory and cardiac morbidity and mortality, increased hospital visits, and a higher risk of adverse birth outcomes [38–42]. It is important to point out that the established standards cannot fully protect human health since there is no safe lower threshold of PM. Strong scientific evidence shows the negative impact of $PM_{2.5}$ exposure on health [39, 43]. Particularly regarding $PM_{2.5}$, long-term exposure to levels above recommended guidelines results in an increase in total, cardiopulmonary, and lung cancer mortality [44–47].

3.2 Urban air pollution in Latin America

Air pollution is the largest and most persistent environmental and public health concern in Latin America and the Caribbean, where socioeconomic gradients among and inequalities within countries aggravate the impact of environmental degradation, generating different patterns of emissions and increasing exposure to pollutants and vulnerability to climate change [48, 49]. The percentage of the urban population in Latin America and the Caribbean is as high as 81%. The region is currently considered the second most urbanized region in the world, after North America [50]. These densely populated areas (medium-sized cities; 1–5 million inhabitants, large cities: 5–10 million inhabitants, and megacities: over 10 million inhabitants) are responsible for a significant amount of pollutants emitted into the atmosphere that does not necessarily remain in urban regions and can be transported over large distances, depending on the type of substance, weather conditions, topographical characteristics, etc. Cities thus contribute to background concentration in the whole hemisphere [49].

The most affected populations are located in urban areas and developing countries. The number and size of megacities in the world have increased dramatically over the last six decades—from 751 million to 4.2 billion in 2018 [49], accounting for 55% of the world population. It has been estimated that by 2050, this percentage may increase to 68% [50].

Megacities are defined as large city metropolitan areas with over 10 million inhabitants [51]. However, megacities also include high-density metropolises where more than 5 million inhabitants work, live, and commute [52]. Three of all 33 megacities, characterized as such according to the latter definition, are located in South America: Rio de Janeiro in Brazil (12.83 million people), Buenos Aires in Argentina (15.02 million), and São Paulo in Brazil (20.83 million). In 2014, megacities accounted for 12% of the world's urban population, while large cities had 8%. In Latin America, Bogotá (Colombia) and Lima (Peru) recently reached 10 million, with 10.6 and 10.4 million inhabitants, respectively. Santiago (Chile), considered a large city, has 6.7 million inhabitants [50, 51].

Few studies have evaluated and compared regional trends of annual concentration of regulated air pollutants in South America. The main obstacles to conducting these comparative studies include the great variability in pollutant measurement techniques and protocols and the difficulty of access to information. In 2013, and for the first time since 1997, data on air pollutant concentration in 21 Latin American cities with more than one million inhabitants were gathered to establish the air quality status (baseline 2011) and trends [53].

It is important to point out that environmental pollution disproportionately affects low- and middle-income countries, with almost 90% of pollution-related deaths occurring in underdeveloped countries. In developed countries, the impact of air pollution is highest among minorities and cities with large underserved populations.

3.3 Air pollution: impact on human health

Air pollution causes a wide range of adverse health effects. As shown by toxicological and epidemiological studies across the world, it is mainly associated with an increase in cardiorespiratory metabolic diseases and cancer morbidity and mortality [54–56]. A number of variables including the use of energy, transportation, and socioeconomic factors play a major role in the generation of air pollutants. The Harvard "Six Cities" study [57] published in the 90's was one of the first to show the lasting positive association between long-term exposure to air pollution and mortality.

Airborne PM enters the body through the skin, eyes, and respiratory mucosa. As to particle size, fine ($PM_{2.5}$) and ultrafine ($PM_{0.1}$) PM are considered the most deleterious to health due to their larger surface-to-volume ratio and thus greater potential to adsorb organic and inorganic compounds [58]. In addition, PM2.5 can penetrate the respiratory tract more deeply, inducing immune cell responses and morphological-functional alterations in the respiratory mucosa.

PM has adverse effects on the respiratory tract, and its main target cells are epithelial cells and lung phagocytes [59, 60]. These fine and ultrafine particles can deposit and remain in the lung alveoli over long periods of time [61]. The mucociliary clearance system is the first line of defense against exogenous agents. Mucus secretion by caliciform cells is an important factor in clearing particles from the airways but can be affected by a number of environmental factors. The latter are the main molecules that induce oxidative stress and subsequent damage to the lung [62].

Among lung phagocytes, alveolar macrophages (AM) play a key role in the biological response to air pollution.

Regarding the chemical composition of PM, metals in PM greatly contribute to the generation of reactive oxygen and nitrogen species (ROS and NOS). The latter are the main molecules that induce oxidative imbalance and subsequent damage to the lung [63–65], heart [66], and liver [67].

In addition to ROS and NOS generation, PM induces alveolar macrophage release of several mediators, including pro and anti-inflammatory interleukins (IL-1, IL-6, TNF-α e IL-10), mitogenic factors, and chemokines [68–70]. These mediators are responsible for tissue immune cell recruitment and activation [71]. This biological response involves activation of intracellular signaling pathways and transcription factors such as NFκB and Nrf2 involved in inflammatory tissue response and regulation of antioxidant genes (phase II detoxification) [72, 73]. Moreover, fine and ultrafine PM can evade this first line of defense and penetrate the alveolar-capillary barrier, thus entering the circulatory and lymphatic systems [74–76] and causing adverse effects at the systemic level and in distant organs.

It has been posited that the mechanisms through which PM exerts systemic effects include—(1) the release of pro-inflammatory and pro-oxidant mediators in the lung; (2) an imbalance in the autonomic nervous system, favoring sympathetic tone through the afferent nerves in the upper airways and/or lung; and (3) passage of ultrafine particles, or of their soluble fraction, to the bloodstream [77, 78]. Of note, one mechanism does not exclude the other, and one or more can be involved. The most relevant health effects of air pollution are induction of oxidative stress, systemic inflammation, endothelial dysfunction, atherothrombosis, and arrhythmia.

Different experimental strategies have shown the presence of soluble components of PM in the liver, kidneys, and heart [79, 80]. In their "Air Pollution and Cardiovascular Disease" report, the American Heart Association concluded that exposure to air pollution is a cardiovascular risk factor [55, 77]. Exposure to particulate matter has both short-term and long-term cardiovascular health effects [75, 81] and reduces life expectancy by months or even years [55, 82, 83].

4. Malnutrition and air pollution in children, a vulnerable population

From a nutrition perspective, the most vulnerable subpopulations are people living in poverty conditions, pregnant women, teenagers, and children in their first childhood period. Because the nutritional status during the prenatal period and childhood is the basis for healthy body growth and overall brain development and is a potential determinant of the presence of comorbidities in adulthood, attention focuses on children under the age of 5 years. In fact, inadequate nutrition is the main cause of death worldwide and accounts for half of all deaths in children under the age of five [84]. Given that nutritional status can affect a person's susceptibility to air pollution, it follows that within the population of children less than 5 years of age, those suffering malnutrition during infancy are the most vulnerable. Forty-five percent of deaths among children aged less than five are associated with undernutrition [85]. The 2019 UNICEF reports on the global nutritional status in infancy worldwide show that at least one in three children under the age of 5 years suffers one or more of the three most visible forms of malnutrition—stunting, wasting, and overweight. Although the global prevalence of stunting among children aged less than 5 years decreased from 1995 million children in 2000 to 149.2 million in 2020, that is, 22% of infants, it is still high. A total of 6.7% of children aged less than 5 years worldwide (45.4 million) suffer from wasting and 5.7% (38.9 million) suffer from overweight.

Given that the child mortality rate is an indicator of the health of a population and that undernutrition accounted for 50% of the 5.2 million deaths among children under 5 in the world in 2019, children with inadequate nutritional status can be considered particularly vulnerable to the adverse effects of air pollution.

Although exposure to airborne pollutants is a health threat to all people across the world, whether living in urban or rural areas, certain populations are particularly vulnerable. Populations identified as being at risk include children, people over the age of 65 years, and subjects with previous cardiorespiratory diseases [86–89].

There is an intuitive understanding that repeated and almost continuous exposure to air pollution in cities synergistically increases the likelihood of acute response and can even exacerbate respiratory diseases, such as asthma, chronic obstructive pulmonary disease, and lung cancer in the overall population and particularly in susceptible populations, including the elderly, subjects with the cardiorespiratory disease, pregnant women, and children under five. However, there is little awareness about the significant impact of air pollution exposure on vulnerable subpopulations, such as malnourished children.

As a result of the combination of physiological, environmental, socioeconomic, and behavioral factors, the health effects of air pollution exposure are more damaging to children than adults. Children are particularly vulnerable during prenatal development and the first years of life since their organs, especially their lungs, are still developing and their immune system is immature. In addition, children have a higher respiratory rate and therefore breathe in a larger volume of air and are exposed to a higher proportion of contaminants than adults. Furthermore, children spend more time outdoors playing or exercising in potentially contaminated environments, and they are closer to the ground where the concentration of certain pollutants can be higher [90–95].

According to the WHO, 286000 children under the age of 5 years died due to exposure to unhealthy levels of ambient air pollution in 2016. Reported statistics show that 93% of children worldwide are exposed to particulate matter ($PM_{2.5}$) levels above WHO air quality recommendations; specifically in middle- and low-income countries in Latin America, this applies to 87% of all children under five [96].

Exposure to air pollution has multiple lung and systemic effects in children. There are numerous studies showing the association between exposure during gestation and the first years of life and the development and/or exacerbation of respiratory diseases, such as asthma and allergies, as well as the incidence of pneumonia and other infectious respiratory diseases [97–99]. In addition, considering that almost 80% of alveoli develop postnatally until about the age of 6 or 7 years and that growth and maturation of the lungs and immune system continue until adolescence, the damage during the first stages of life is a determinant of lung function in later life.

As to the cardiac effects in children and adolescents, exposure to air pollution is associated with systemic inflammation, an increase in vasoconstriction molecules, an increase in arterial blood pressure, and changes in sub-clinical atherosclerosis markers, such as arterial stiffness and increase in carotid intima-media thickness, all of which can predispose to early onset of cardiovascular disease [100–102].

Worldwide, malnutrition is strongly associated with up to 19% of childhood deaths and contributes significantly to reducing life expectancy [16]. While sub-chronic nutritional deficiencies are not immediately life-threatening, these deficiencies increase susceptibility to other challenges resulting in additive and synergistic reductions in health [7]. It has been shown that exposure to ambient air pollutants is associated with concurrent poor nutritional status [103, 104]. Regarding undernutrition and air pollution, a recent study conducted by our research group using an animal model of nutritional growth retardation (NGR) showed that acute exposure to Residual Oil Fly Ash (ROFA), a substitute for ambient air pollution, causes alterations in the lung and also in distant organs, including blood vessels, heart, and liver. NGR animals showed inflammation and an ensuing decrease in alveolar space; moreover, *in vitro* tests showed that response to ROFA was lower in alveolar macrophages obtained from ROFA-NGR animals. As regards the heart, exposure to ROFA caused oxidative stress and alterations in blood vessel biochemical markers, which might be associated with heart contractility failure. Evaluation of ROFA effects on the liver showed an increase in the number of lymphocytes in the liver parenchyma and of binucleated hepatocytes; the latter parameter is associated with hepatic regeneration as a response to toxic tissue damage triggered by xenobiotic or dietary-induced liver damage. Our results highlight the key role of nutritional status in the ability to respond to air pollutants [11, 81, 105–108].

5. Discussion

It is important to understand child malnutrition as a public health problem that threatens future generations. It is equally important to understand that the children of today are the adults of tomorrow, and ensuring nutrition safety can therefore break the vicious intergenerational cycle whereby malnutrition perpetuates poverty and poverty perpetuates malnutrition.

Environmental factors, including climate and geographical conditions, and social-economic factors are determinants of production, availability, and access to food. Because a person is a social being in constant interaction with the environment, air pollution is not merely a factor that could add to malnutrition aggravating the baseline condition but is a causal factor of malnutrition.

The United Nation's Sustainable Development Goals (SDG) acknowledge the importance of social and environmental factors as determinants of health. All SDG are clearly linked to health-related goals and reflect an increasing awareness of the interrelation among health objectives, environmental targets, and goals to end poverty. SDG aims to guarantee a healthy life for all (Goal 3) and to make cities inclusive, safe, resilient, and sustainable (Goal 11) [109].

Despite substantial detrimental health, economic, and environmental effects, the morbidity burden associated with pollution worldwide has been underestimated and has therefore not been set as a high priority on international development agendas and in global health policies.

It is noteworthy that air pollution increases the risk of developing a number of lungs, cardiovascular, liver, and brain diseases. Other environmental factors such as temperature, noise, stress, electromagnetic fields, and built-up environments like cities also contribute to the risk of developing these diseases. Air pollution and environmental contamination—both aggravated by farming practices and other anthropogenic sources of pollution—increase global mortality and morbidity.

6. Conclusions

Among other factors, susceptibility to various diseases is influenced by the vulnerability. In this context, infants, aggravated by their nutritional status, are one of the most fragile and unprotected populations. The health effects of contamination known today may be just the tip of the iceberg. In the light of the evidence shown here, efforts to reduce exposure to air pollutants must be intensified urgently and must be endorsed by adequate and effective legislation.

Increasing the population's awareness about the vast and terrible effects of ambient and household air pollution on the health and life expectancy of children is vitally important and must not be underestimated.

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Conflict of interest

The authors declare no conflict of interest.

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Chapter 11

Perspective Chapter: Sugar and Its Impact on Health

Roberto Ordoñez-Araque and Byron Revelo-Vizuete

Abstract

Consumption of foods containing free or added sugars continue to increase, causing the global prevalence of noncommunicable illnesses to rise year after year. The purpose of this chapter is to highlight the issues associated with excessive sugar consumption. The biochemical description of the major monosaccharides, disaccharides, and polysaccharides in the diet, as well as their metabolism and absorption in the organism, will be used to objectively understand how most of the carbohydrates we eat, regardless of their name, end up being used in the glycolysis pathway to produce energy. Excess sugar consumption will be converted to triglycerides and cholesterol in the body through de novo lipogenesis, increasing the prevalence of overweight and obesity, as well as other diseases. The necessity of eating fruits and vegetables with their matrix will also be emphasized, as these are linked to weight loss and obesity prevention. This does not include 100 percent natural juices, because when their matrix is broken, sugars are released and they act as sugary drinks, as well as food made with refined flours or white rice because the starch is quickly decomposed into glucose in our bodies because they are not accompanied by fiber.

Keywords: carbohydrates, metabolism, absorption, non-communicable diseases, public health

1. Introduction

The prevalence of non-communicable diseases (NCDs) in the world is the highest it has ever been, both in developed and developing countries. The main risk factors for these diseases are poor diet and lack of physical exercise, with NCDs claiming the lives of 41 million people a year [1]. High consumption of free sugars is associated with obesity, overweight, and a high risk of non-communicable diseases [2]. For this reason, society must understand the risk of high sugar consumption, since people do not understand the metabolism of these biomolecules and how, regardless of the name given to the sugar, it will have the same metabolism in our body.

This is why it is important to understand the metabolic pathways that occur in our bodies when we eat carbohydrates. In general terms, glucose is used by our body to produce energy through the metabolic pathway of glycolysis. Fructose enters the body and is metabolized in muscle, adipose tissue, and liver to become part of glycolysis. Galactose is an epimer of glucose and through the galactose-glucose interconversion pathway enters glycolysis [3].

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All sugars end up in the glycolysis cycle behaving like glucose; that is, all sugars end up metabolized in the same way. When sugar consumption is exceeded, it will be converted into pyruvate as the final product of the glycolysis pathway and from this, lactate or acetyl-CoA molecules can be formed. From the acetyl-CoA molecule, the organism can synthesize triglycerides and cholesterol through the biochemical route of de novo lipogenesis [4]. That is to say, all the free sugar or starch without fiber that enters our organism can end up being stored as fat in our adipose tissue or can be converted into low-density lipoproteins (LDL).

The consumption of sugar through the intake of vegetables is not associated with any pathology and can be eaten freely since it is consumed in its matrix and sugars are accompanied by all the fiber and other nutrients, this causes them to be assimilated very slowly, while the starch when it is not accompanied by the entire matrix of the food (fiber, vitamins, minerals, organic acids, etc..), such as refined flours, is quickly metabolized and absorbed by the body in the form of glucose, which is why people who eat foods made with refined flours (white bread, rice, pasta, etc.) are consuming sugar.

In the same way, the consumption of 100% natural juices should be avoided, since not being in its matrix at the time of processing, all the sugar is released and these juices become very similar to sugary drinks in terms of sugar content [5, 6].

This chapter aims to disclose the problems associated with excessive sugar consumption, to develop an understanding of how it behaves in our body and which sugar foods can be potentially unhealthy to consume.

2. Carbohydrates

Carbohydrates are molecules formed by several alcohol groups together with one more oxidized carbon (carbonyl group). The main functions of carbohydrates are the energy source for the cell, energy reserve in tissues (liver and muscle), a structural molecule in several tissues, and precursor for the formation of different biomolecules (anaplerotic pathways) [7]. The classification of carbohydrates is as follows.

2.1 Monosaccharides

The simplest carbohydrates are called monosaccharides. A simple sugar or monosaccharide consists of a carbon chain, hydroxyl groups, and an aldehyde group (aldose) or a ketone group (ketose). They are classified according to the number of carbons into trioses and tetroses (metabolic intermediates), pentoses and hexoses (most important monosaccharides), heptoses (formed during photosynthesis), and octoses. Their chemical nature will allow having different types of monosaccharides, for example, there can be aldohexoses and ketohexoses. Their stereoisomerism is also important since they can present asymmetric carbons, and thanks to this a great number of monosaccharides can be formed, so we can name the most important monosaccharide: glucose, which can exist in the D and L form (configuration of the asymmetric carbon atom that is farther away from the aldehyde group) [8, 9].

With this same classification we can include D sugars that have a difference in their configuration only in one carbon atom, these are known as epimers, for example, D-glucose and D-galactose (epimers), they are only different in the configuration in carbon 4 [10].

The most important monosaccharides in the world of nutrition are hexoses. The main one is glucose ($C_6H_{12}O_6$), A molecule that provides energy to the cells of all living beings, it is the main monomer of the disaccharides and polysaccharides, and is formed by plants during photosynthesis. One of the main characteristics of glucose is its rapid assimilation into the organism; it is absorbed by specific transporters and is also the substrate used by several microorganisms for fermentation. Fructose ($C_6H_{12}O_6$), is found mainly in fruits (origin of its name), it does not need insulin for its metabolism. Galactose ($C_6H_{12}O_6$), a monosaccharide that in the liver is converted into glucose to form part of the energy reserves, this is synthesized in the mammary glands of mammals; its contribution through the diet will be from the intake of milk [11, 12].

2.2 Disaccharides

Disaccharides are formed when two monosaccharides are connected by a covalent bond, this is known as a glycosidic bond, this bond can be of the α or β type depending on the configuration of the anomeric carbon atom of the bond. In general, this anomeric carbon atom is present in only one of the two monosaccharides that will form the final bond, for this reason, the final molecule still has a free aldehyde or ketone group and can behave as reducing sugar. The exception to this rule is sucrose since its two anomeric carbon atoms are bonded together [9, 13].

The most important disaccharides in nutrition are sucrose, which is a disaccharide formed by a bond between the anomeric carbon 1 of glucose and the anomeric carbon 2 of fructose (bond β $(2 \rightarrow 1)$). It is known as table sugar and is mainly processed from sugar cane or beet. It is the most widely consumed sugar and is associated with processed and ultra-processed foods. Lactose is known as the milk sugar formed by the union of the anomeric carbon 1 of D-galactose with the anomeric carbon 4 of D-glucose, forming a β $(1 \rightarrow 4)$ bond (lactose can undergo mutarotation presenting two isomers: α and β). Maltose is a disaccharide resulting from the bonding of two glucose units at carbon 1 and 4, the anomeric carbon atom is in the α-form configuration, and thus forms an α $(1 \rightarrow 4)$ bond [13, 14].

2.3 Oligosaccharides and polysaccharides

Oligosaccharides are short chains of monosaccharides (up to 10 monomers) that are formed by glycosidic bonds, proteins (glycoproteins), or lipids (glycolipids) that can also be formed to these chains. One of the most famous oligosaccharides in nutrition is maltodextrin, obtained from the hydrolysis of starch and possessing between 5 and 10 glucose units, it is used in many processed foods and indifferent food mixtures, supplements, and medicines. It is rapidly metabolized in the body [15].

Polysaccharides are characterized by their large molecular size, insoluble in water, form colloidal solutions, and their bitter taste, unlike disaccharides and monosaccharides which have a sweet taste. Generally, their bonds are formed between the anomeric carbon and the hydroxyls found in carbons 4, 6, and 3. When there is an excess of glucose intake, animals store it in the form of glycogen (branched polysaccharide), when the organism requires energy, this reserve is released in the form of glucose to produce energy. In the food diet, mainly when we talk about malnutrition, the polysaccharide of greatest interest is starch. Starch is made up of two types of chains: amylose, the major component of starch, are linear chains formed by D-glucose that are formed by α bonds $(1 \rightarrow 4)$ and generally have a helical spatial structure. And of amylopectin: chains of branched order that are composed of α (1 → 4) bonds in their linear part, and α (1 → 6) bonds in the branches [9, 14].

3. Carbohydrate metabolism

3.1 Glucose metabolism

Sugar in the human body is metabolized from the metabolic pathway of glycolysis in the cytoplasm, this pathway aims to convert one molecule of glucose into two molecules of pyruvate, and this can be converted into lactate, ethanol, or acetyl-CoA (a molecule that can enter the citric acid cycle or substrate for the formation of fatty acids, ketone bodies, and cholesterol) [16].

In glycolysis glucose by the enzyme, hexokinase is phosphorylated by ATP to glucose-6-phosphate with a molecule of ATP, this is transformed into fructose-6-phosphate by the action of phosphoglucose isomerase (here an aldose is converted into ketose). ATP together with the enzyme phosphofructokinase phosphorylates fructose 6-phosphate to fructose 1,6-bisphosphate and ADP. The enzyme aldolase catalyzes the cleavage of fructose 1,6-bisphosphate which has six carbons into two molecules with three carbons respectively: glyceraldehyde 3-phosphate (only this molecule will follow in glycolysis) and dihydroxyacetone phosphate (this molecule can be converted to aldehyde 3-phosphate by the action of triosephosphate isomerase). The enzyme glyceraldehyde 3-phosphate dehydrogenase catalyzes the reaction of glyceraldehyde 3-phosphate to 1,3-bisphosphoglycerate using inorganic phosphate and NAD+. The phosphoryl group of 1,3-bisphosphoglycerate is transferred to ADP to generate ATP along with the 3-phosphoglycerate molecule via the enzyme phosphoglycerate kinase, this molecule is converted to 2-phosphoglycerate by the action of phosphoglycerate mutase. The 2-phosphoglycerate is dehydrated to form phosphoenolpyruvate by the action of the enolase enzyme converting the low-energy phosphate ester bond into a high-energy bond. Finally, the enzyme pyruvate kinase causes the irreversible transfer of the phosphoryl group from phosphoenolpyruvate to ADP forming ATP and pyruvate (see **Figure 1**) [16–18].

3.2 Fatty acid metabolism from glucose: de novo lipogenesis

One of the major problems of eating foods with excess free sugars is that glucose metabolism will trigger the conversion of this excess into fatty acids.

Lipogenesis is the synthesis of fats (triglycerides) in the liver and adipose tissue. De novo lipogenesis is a biochemical pathway capable of converting carbohydrates into triglycerides when glycogen stores are full. Fatty acids can be synthesized through an extramitochondrial system where complete synthesis of palmitate from acetyl-CoA occurs in the cytosol (aqueous substance surrounding the nucleus and organelles of the cell), in most mammal's glucose will be the main substrate for de novo lipogenesis to occur. In general, when there is a high availability of ATP and acetyl-CoA (accompanied by a low rate of the tricarboxylic acid cycle, better known as the Krebs cycle - citric acid cycle), the body can synthesize fatty acids, using acetyl-CoA as the carbon source that comes mainly from carbohydrates and even from ketogenic amino acids [20, 21].

As mentioned above, pyruvate is obtained from glucose in the mitochondrion and can be converted to acetyl-CoA, which must be transferred to the cytosol. This occurs

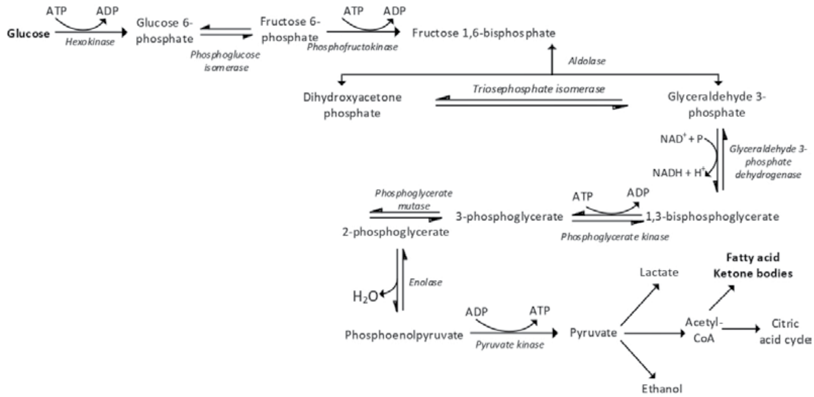

Figure 1.
The pathway of glycolysis. Modified from: Hames and Hooper [19].

due to its condensation with oxaloacetate to form citrate. The citrate in the cytosol is regenerated back to acetyl-CoA and oxaloacetate by the enzyme ATP-citrate lyase (oxaloacetate returns to the mitochondrial matrix as it is converted to malate and pyruvate), the energy generated is used in fatty acid synthesis.

Acetyl-CoA undergoes carboxylation to form malonyl-CoA (reaction catalyzed by the enzyme acetyl-CoA carboxylase using biotin as a prosthetic group). Both acetyl-CoA and malonyl-CoA are converted to their ACP (acyl carrier protein) derivatives. These compounds will have an elongation pathway: 1) Condensation of acetyl-CoA and malonyl-CoA into acetoacetyl-CoA (together with the release of free CoA and CO2) by the enzyme acyl-malonyl-CoA. 2) Reduction by NADPH forming D-3-hydroxybutyrate-ACP (reaction catalyzed by β-ketoacyl-ACP reductase enzyme). 3) Dehydration to crotonyl-ACP (the enzyme acting is 3-hydroxy acyl-ACP). 4) Reduction by NADPH which forms butyryl-ACP (thanks to the action of enoyl-acyl carrier protein reductase). As this happens there are several successive rounds of elongation that add more carbon atoms to the hydrocarbon chain that is growing from the malonyl-ACP, this happens until palmitate (16-carbon fatty acid - C16,0) is formed [20, 22].

Similarly, animals can synthesize cholesterol from acetyl-CoA from a series of reactions that will form the 27 carbon atoms of cholesterol (acetate units are converted to five-carbon isoprene units, which condense to form the linear precursor of cyclic cholesterol). Although the body needs cholesterol for its daily functions, an excess of cholesterol-containing low-density lipoproteins can lead to atherosclerosis (hardening of the arteries due to the presence of cholesterol, which causes arterial thickening) [23].

People, in general, do not realize that excessive sugar consumption can increase triglyceride, cholesterol, and LDL levels, which can lead to several pathologies starting with overweight and obesity. Many doctors, upon seeing laboratory tests with high levels of these markers, prohibit the intake of fat in the diet, when the first thing that should be prohibited is the intake of foods with free sugars in their composition (see **Figure 2**).

3.3 Fructose metabolism

As already mentioned, fructose is one of the most consumed sugars in the human diet, since it is present in countless fruits and is the molecule that, together with

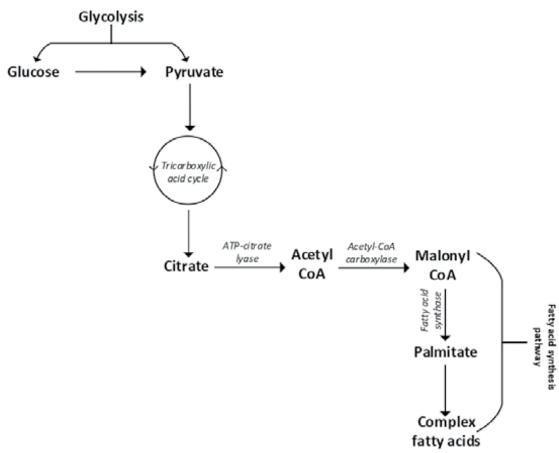

Figure 2.
De novo lipogenesis. Modified from: Ameer et al. [20].

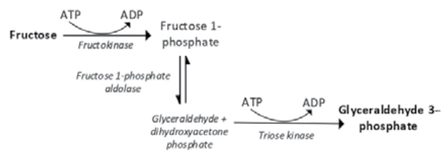

Figure 3.
The pathway of fructose. Modified from: Hames and Hooper [19].

glucose, forms part of sucrose. Fructose can be metabolized in the muscle, adipose tissue, and liver. When metabolism occurs in muscle and adipose tissue, it is phosphorylated by the enzyme hexokinase to form fructose 6-phosphate, which then becomes part of glycolysis [3].

While when it is metabolized in the liver, the enzyme glucokinase interacts instead of hexokinase, with the disadvantage that the enzyme is only capable of phosphorylating glucose. For this reason, fructose enters the fructose-1-phosphate pathway. The pathway starts with the enzyme fructokinase which converts fructose to fructose-1-phosphate, this is then cleaved from fructose-1-phosphate into glyceraldehyde and dihydroxyacetone phosphate (a molecule that enters glycolysis in the triose phosphate isomerase step). Finally, glyceraldehyde is phosphorylated by the action of triose kinase to glyceraldehyde 3-phosphate and thus can also enter glycolysis (see **Figure 3**) [3, 24].

3.4 Galactose metabolism

Galactose is one of the monomers from which lactose is formed, and is an epimer of glucose (they differ in the carbon 4 configuration). Galactose will enter glycolysis, but it must first undergo an epimerization reaction via the galactose-glucose interconversion pathway.

This pathway begins with the enzyme galactosidase which phosphorylates galactose to produce galactose 1-phosphate, this molecule is catalyzed by the action of the enzyme galactose-1-phosphate uridylyltransferase, transferring a uridyl group from

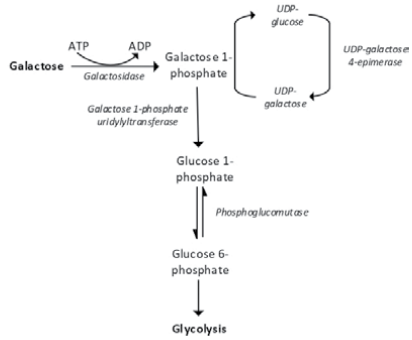

Figure 4.
The pathway of galactose. Modified from: Hames and Hooper [19].

uridine diphosphate glucose (UDP-glucose) to galactose 1-phosphate, and thus forming uridine diphosphate galactose (UDP-galactose) together with glucose 1-phosphate. UDP-galactose is converted to UDP-glucose by the action of the enzyme UDP-galactose 4-epimerase. Finally, glucose 1-phosphate is converted to glucose 6-phosphate by catalysis of the enzyme phosphoglucomutase to enter glycolysis [25, 26].

After understanding how dietary monosaccharides at the end of the metabolic pathways behave in the same way, as they access glycolysis to generate energy and their excess in unhealthy molecules in our organism, we must understand how they enter our body, and how by consuming some starch-rich foods we end up consuming free glucose indirectly (see **Figure 4**).

4. Digestion of carbohydrates

Carbohydrate digestion is a complex system that starts from the mouth. In this case when ingested through the diet: starch, glycogen, or glucose polymers, these will begin to break down by the action of the enzyme $\alpha(1 \rightarrow 4)$ glycosidase (salivary amylase) that is present in the saliva, this enzyme partially degrades the linear chains of amylose and those present in amylopectin, thus beginning to break down the starch. This action is not very extensive since it will be prolonged during the time that the food is in the mouth, the enzyme accompanies the food and is denatured when it enters in contact with the acid pH of the stomach [27, 28].

Digestion continues in the duodenum (first portion of the small intestine), here the enzyme α-pancreatic amylase is found, which is synthesized by the pancreas and has the same action as salivary amylase. At this point the starch molecules and other polymers formed, will be metabolized to oligosaccharides, mainly to: maltose, maltotriose, and in limit dextrins (oligosaccharides of approximately 8 glucose units branched from starch amylopectin and glycogen containing α(1–6) branch points that cannot be cleaved by α-amylase enzymes).

Finally, hydrolysis to monosaccharides of all oligosaccharide and disaccharide molecules that were formed by α-amylases and of disaccharides that are naturally ingested in the diet occurs through the action of several oligosaccharides and disaccharidase enzymes found in the enterocyte apical membrane [27, 29]. **Table 1** shows the main enzymes that break glycosidic bonds in the body.

Secretion and origin	Enzymes	Substrate	Action	Products
Saliva from the salivary glands of the mouth	α-amylase	Starch / α-linked polysaccharides	Hydrolysis	Dextrins - maltose
Exocrine secretions of pancreatic acinar cells (site of action: duodenum)	α-amylase	Starch and dextrins	Hydrolysis	Dextrins - maltose
Small intestine (brush border membrane)	Saccharase	Sucrose	Hydrolysis	Glucose - fructose
	α-dextinase (siomaltase)	Dextrin - isomaltose	Hydrolysis	Glucose
	Maltase	Maltose	Hydrolysis	Glucose
	Lactase	Lactose	Hydrolysis	Glucose - galactose

Adapted from the book: Krause. Diet Therapy [27].

Table 1.
Enzymes that allow starch and glucose polymers to be rapidly broken down into oligosaccharides, disaccharides, and monosaccharides during digestion.

5. Free and intrinsic sugars

Everyone needs to understand the difference between free sugars and intrinsic sugars. According to the World Health Organization in its Guideline: Sugars intake for adults and children, free sugars are all monosaccharides and disaccharides that the food industry intentionally adds to their products, and sugars that are found naturally in different foods such as honey, 100% fruit juices, syrups, etc.

While intrinsic sugars are those found in whole vegetables, i.e. unprocessed fruits and vegetables, these types of sugars are not related to any adverse health effects, while free sugars are associated with several pathologies as we will describe later in this chapter [2].

The industry tries to create new products and often masks free sugars with different names unfamiliar to people (including honey, which has about 80% free sugars in its composition) [30], **Table 2** shows some of the names under which sugar is labeled in some food products.

6. Food matrix (starch can also be sugar)

The matrix of food is the global structure that a food has, it is the support and the joint union of all the nutrients of which it is constituted, this union allows us to identify each food with a certain thickness, texture, density, hardness, color, porosity, crystallinity, etc. Each food in nature has its matrix that provides certain characteristics when consumed, such as the bioavailability of nutrients or the sensation of satiety (solid foods rich in fiber will provide more satiety than liquid or semi-solid foods [32].

During the processing of food (industrial or at home), there will be a release of nutrients on a large scale since its matrix (its global structure) is being broken, this will allow the slow metabolism and absorption that the molecules had before to become much faster. In case of sugars, they will go from being intrinsic to free and will be absorbed immediately, since the organism will not have to use biochemical mechanisms to break the matrix, which in many cases can pass through the stomach

Other names for sugar that you may see on food labels		
Agave nectar	Evaporated cane juice	Maltodextrin
Brown sugar	Fructose	Malt syrup
Cane crystals	Fruit juice concentrates	Maple syrup
Cane sugar	Glucose	Molasses
Corn sweetener	High-fructose corn syrup	Raw sugar
Corn syrup	Honey	Sucrose
Crystalline fructose	Invert sugar	Syrup
Dextrose	Maltose	

The food industry uses other names instead of sugar to deceive the consumer. Source: Harvard T.H. Chan School of Public Health [31].

Table 2.
Compounds are formed by different monosaccharides that provide a sweet taste and their final metabolic effect in the organism is the same as glucose.

and intestine intact since the structure can be accompanied by fiber (polysaccharide not digestible by the human body) [33].

All sugars or starch in the organism will be metabolized as monosaccharides (glucose, fructose, and galactose). It will depend on the dietary intake for this to be fast or slow when starch is consumed that is not accompanied by its fiber matrix, the absorption will be fast, this group includes refined flours, with which countless products can be made such as bread, white rice and pasta [34, 35]. Consuming this type of food is the equivalent of eating monosaccharides (sugar). Precisely many of these products may be accompanied by more components that are not recommended for a healthy daily diet, for example, bread made with refined flours has as ingredients: sugar, salt, and generally trans fats. People should be aware that just because a food does not have a sweet taste, such as white rice, does not mean that it does not have glucose in its composition [36].

7. Health problems due to consumption of free sugars

Current evidence indicates that the consumption of free sugar through food is associated with several diseases, observational studies have shed several lights on the problems associated with sugar consumption, so we can find relationships between the intake of sugar-sweetened beverages with the association of adverse effects on markers of cardiovascular risk, especially in the increased risk of stroke [37], or we can cite the analysis conducted in 75 countries where the relationship between the consumption of sugar-sweetened soft drinks and its positive association with the prevalence of overweight, obesity, and diabetes was found, these data do not vary regardless of the income of the household [38].

It is also interesting to cite the study in which 26,190 people without pathologies (diabetes and cardiovascular diseases) were followed for 17 years, in this case, it was associated that people who consumed more than 15% of their energy intake from sucrose intake in their meals and drinks could be more likely to have coronary events [39]. Although observational studies often do not provide the real causality of the results, there are intervention studies that present the same conclusions on sugar consumption, for example, a meta-analysis of randomized controlled trials and cohort studies showed that the consumption of free sugars in food and sugar-sweetened beverages is the most important and determining factor in weight gain, while people who reduce sugar consumption show a decrease in body weight [40].

Another meta-analysis and cohort study conducted in children and adults indicated that consumption of sugar-sweetened beverages is associated with increased body mass index, whereas reduction of these beverages showed a reduction in weight gain especially in children (an interesting conclusion was that reduction of sugar-sweetened beverages in children causes more effect on weight loss than school-based good nutrition programs) [41].

The relationship of dietary sugar intake on blood pressure and serum lipids has also been analyzed in a meta-analysis of randomized controlled trials. The conclusions found a positive association, including this association regardless of the bodyweight of the person, which indicates that it is not always necessary to be overweight or obese and to be prone to suffer from diseases associated with sugar consumption [42]. Finally, we can refer to a study carried out after six years of follow-up where the quantity and quality of abdominal adipose tissue were analyzed using a consumption frequency questionnaire, data were obtained on the consumption of sugar-sweetened beverages and their association with the change in the volume of visceral adipose tissue, while consumers of diet drinks were also analyzed, which were not associated with changes in abdominal adipose tissue [43].

It should also be mentioned that several studies have determined that the consumption of foods with sugars in their composition is highly related to the increased risk of dental caries since different bacteria found in the mouth are capable of transforming monosaccharides into acids that will subsequently affect dental enamel [44].

To complement all this information we can refer to the most current report of the European Food Safety Authority (EFSA) [45], which was developed following the request to establish a maximum tolerable sugar intake level by 5 countries. Although EFSA does not make guidelines or recommendations that influence public health, it does give nutritional conclusions based on scientific evidence, for this reason, the scientific experts analyzed 120 scientific studies (the scientific publications that were analyzed met different inclusion criteria, these were selected from more than 25,000 studies in 2018 and 7500 in 2020) that linked the intake of sugars in the diet with chronic metabolic diseases, and pathologies that were related to pregnancy and tooth decay. This meta-analysis concluded that it is not possible to establish a maximum tolerable intake level, nor a safe level of dietary sugar intake. This is because after the analysis of all the research and with the available scientific evidence, it can be determined that the intake of free and added sugars should be as low as possible. After all, it is associated with chronic metabolic diseases and tooth decay, the consumption of sugar is not essential because what the body needs can be consumed in fruits if they are accompanied by their matrix, for this reason, there should not be a recommendation.

The World Health Organization (WHO) already pronounced this issue in 2015, likewise, after the analysis of randomized controlled meta-analyses in adults and children, concluded that the consumption of free sugars should be reduced throughout the life cycle. This consumption should not be more than 10% of total caloric intake and it is recommended to reduce this consumption to 5% [2]. **Table 3** presents the metabolic diseases related to the consumption of different types of sugar and the pathologies related to obesity.

Metabolic diseases	Sugar type	Obesity-related pathologies
Obesity	Free and added sugars, sweetened beverages, and 100% fruit juices	All causes of death (mortality), hypertension, dyslipidemia, type 2 diabetes, coronary heart disease, stroke gallbladder disease, osteoarthritis, sleep apnea and breathing problems, low quality of life, mental illness such as clinical depression, anxiety, and other mental disorders, body pain and difficulty with physical functioning and many types of cancer: Meningioma (cancer in the tissue covering the brain and spinal cord), adenocarcinoma of the esophagus, multiple myeloma (cancer of blood cells), kidneys uterus, ovaries, thyroid, breast (postmenopausal women), liver, gallbladder, upper stomach pancreas, colon and rectum
Liver diseases	Free and added sugars, sweetened beverages, and sugar-sweetened beverages	
Diabetes type 2	Free and added sugars, sugar-sweetened beverages, and 100% fruit juices	
LDL cholesterol	Free and added sugars and sugar-sweetened beverages	
Hypertension	Free and added sugars and sugar-sweetened beverages	
Cardiovascular diseases	Fructose and sugar-sweetened beverages	
Gout	Fructose, sweetened beverages, and 100% natural juice	
Diabetes during pregnancy	Sweetened beverages	

LDL: Low-density lipoprotein. Information was obtained after the evaluation of 120 meta-analyses selected from more than 32,000 studies from 2018 and 2020 after meeting inclusion criteria. Excessive sugar consumption is related to overweight and obesity, in turn, this disease is associated with other pathologies.
Adapted from: EFSA explains draft scientific opinion on a tolerable upper intake level for dietary sugars [45] and Centers for Disease Control and Prevention: Cancer and obesity [46].

Table 3.
Relationship between sugar consumption and health problems.

8. White rice and refined flours

Throughout the chapter, the health problems that the consumption of free sugars can cause have been described, but it must be taken into account that many times people assume that the consumption of rice and flour does not mean eating sugar. As already mentioned, rice and flours are formed by starch, starch is formed by amylose and amylopectin which are linear and branched chains of glucose, if foods that are obtained from flour or rice, are not accompanied by their matrix, the degradation and absorption of glucose in the body will be rapid, and therefore the intake of this type of food will be very similar to the consumption of products with free sugars. Whole rice is composed of an outer layer which is responsible for wrapping the grain, the bran (made up of pericarp, this or integument, and aleurone layers), the germ, and the endosperm (here the reserve nutrients are stored: starch) [47].

In general, white rice is not important from the point of view of nutrition, since the germ and the bran (which contains mainly fiber in its composition) are removed in the process of production. For this reason, white rice has been the subject of several investigations and is related to the increased risk of type 2 diabetes (during consumption a large amount of glucose is obtained in a very short time after the metabolism of starch, with this there is a significant increase in blood glucose, causing the pancreas to secrete a high amount of insulin. When this process is repeated throughout life, insulin resistance can develop) [48], it is also important to note that replacing white rice with brown rice in the diet is associated with a decreased risk of type 2 diabetes [49].

If we talk about flour, we can use wheat as an example (in flour we can include all cereals, and in general there can be whole wheat flour and refined flour), which is composed of bran (pericarp, testa, and aleurone), germ and endosperm (main component composed of starch as in all cereals) [50]. Like rice, refined flours are composed mostly of starch and are not accompanied by fiber, which will cause the same outcome of glucose absorption after consumption, for this reason, the consumption of refined cereals is associated with a higher incidence of metabolic syndrome (group of risk factors for heart disease, diabetes, and other pathologies) [51], and among the most important problems of high consumption of refined grains in the long term is their association with the risk of coronary heart disease [52].

9. Natural fruit juices (naturally sweetened)

As already mentioned in Section 6 of this chapter, it is important to consume food in its matrix, when we break this matrix, we release nutrients that will be much faster to absorb in our organism. Fruit juices 100% natural are no exception, if we break the matrix of fruit, we release all the sugars it may have (fructose, glucose, sucrose, etc.,) and these will go from intrinsic to behave as free sugars, behaving like any sugary drink [53]. In the United States, fruit juices have been ranked 5th of the 6 beverages recommended for consumption according to their health risks and benefits, with water ranked first and sugar-sweetened beverages sixth [54].

There is ample evidence on 100% natural fruit juices, their health implications can be seen in **Table 3**, these associations to different pathologies have been collected for years, so there are meta-analyses that indicate that the intake of sugary drinks and fruit juices have a high association with the possible development of type 2 diabetes, and conclude that the consumption of fruit juices is not a healthy alternative to sugar-sweetened beverages [55].

Type 2 diabetes is the pathology that is most related to excessive consumption of fruit juices, has a high association when analyzed in a large number of people, so it is emphasized that nutritional recommendations should be followed to reduce the consumption of natural juices in the diet [56]. Sugar is one of the main causes for overweight and obesity, that is why the consumption of fruit juice is closely related to these pathologies since in its composition it has as many free sugars as a sugary drink, the metabolism of fruit is not the same as that of juice, there is no feeling of satiety since it is not chewed, in the juice there are several servings of fruit that are consumed immediately, raising blood glucose levels just as a drink with glucose, fructose or sucrose does, it is also important to mention that in fruit juices an interesting amount of fiber is lost during processing [57]. We can also mention three prospective cohort studies where the relationship of changing the consumption of sugary drinks and fruit juices with water in the long term was examined, finding a positive association, that is, if in the diet the consumption of sugary drinks (including juices) is changed by water, a marked decrease in weight is observed, it is important to emphasize that water does not have compounds that intervene in the metabolism of a person to lose weight, but the simple consumption of water prevents people from consuming unhealthy beverages [58]. Finally, it should be mentioned that the consumption of natural juices is associated with dental caries in adults, which has been corroborated in several studies [59, 60].

For this reason, one of the nutritional guidelines in the world is the reduction of this type of beverage, but the lack of knowledge of people about sugar leads them to think that 100% natural juices are a good nutritional alternative, this can be corroborated in a study conducted in California with data from 2003 to 2009 in children, where it was identified that during those years the intake of sugary drinks decreased drastically but the consumption of 100% natural juices increased in the same way [61].

10. Fruits: The only sugar we need

The human body needs glucose to properly perform its daily functions, this sugar is found in fruits and vegetables intrinsically accompanied by its matrix. For this reason, we can eliminate the consumption of free sugar (remember that one of the WHO recommendations is not to exceed 5%, while the EFSA does not suggest any limit since its consumption is associated with several pathologies). The WHO is one of the most important recommendations it has given in the area of nutrition is that a healthy diet should include the consumption of 5 servings (at least 400 grams) of fruits and vegetables per day (this recommendation does not include starchy tubers such as potatoes, sweet potatoes, cassava, etc.), its recommendations are based on scientific evidence and emphasize that eating 5 servings of fruits and vegetables per day can reduce the risk of the onset of noncommunicable diseases [62].

It should also be clarified that the intake of fruit juices does not replace fruit consumption under any circumstances, even though the fruit juice industry tells us otherwise. It is interesting to mention that the consumption of vegetables (mainly fruits) not only does not cause overweight and obesity but also is associated with the prevention of these pathologies [63]. It has been found that the consumption of fruits and vegetables has a positive relationship with the improvement of anthropometric parameters and the risk of increased body adiposity, for this reason, nutritional and governmental agencies should seek all the necessary mechanisms for people to increase the consumption of fruits and vegetables [64].

For this reason, nutrition is increasingly seeking to find the best way to convey healthy guidelines to the population and the nutritional pyramid that has been used for many years is increasingly in disuse because its interpretation can cause several nutritional errors, for this reason, the new trend proposed by one of the best schools of nutrition in the world is the healthy eating plate (the Harvard plate) where the interpretation is clear and simple, no superfluous foods without nutritional importance (sugary drinks, alcoholic beverages, desserts, sausages, trans fats, etc.) and it is established that the main pillar of the nutritional pyramid is the healthy eating plate,) and it is established that the fundamental pillar of nutrition is fruits and vegetables [65].

11. Conclusions

It is important for the whole society to understand in a general way the metabolism of sugar in the human body, this will allow people to make better decisions when choosing their food since they will understand what type of nutrients are found in the products and if they are recommended or not.

Glucose is the main monomer of carbohydrates, the body uses it to generate energy, its excess is stored as glycogen in the liver. Fructose and galactose (important monosaccharides in the diet) are metabolized in the body, generating compounds to enter the glycolysis pathway. Once the glycogen reserves are completed, pyruvate (molecule resulting from glycolysis) can be transformed into the acetyl-CoA molecule, and this in turn is used by the organism to generate fatty acids and cholesterol. In other words, the excessive consumption of carbohydrates can be transformed into adipose tissue in the body.

Sugar should always be consumed in the food matrix (intrinsic sugar), i.e., accompanied by all the fiber and other nutrients. When food is processed, sugar is released and behaves as free sugar, i.e. like any sugary drink or any processed or ultra-processed food with sugar or refined flours in its composition.

Excessive sugar consumption is associated with several non-communicable diseases, starting with overweight and obesity. A strong association of pathologies has been found after the consumption of free or added sugar in the diet, among the most important ones: Liver diseases, type 2 diabetes, cholesterol (LDL), cardiovascular diseases, hypertension, gout, and gestational diabetes.

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Conflict of interest

The authors declare no conflict of interest.

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Chapter 12

Malnutrition: The Tripple Burden and the Immune System

Ohanube Goodluck A.K., Agimogim Kelvin Ojong and Ikeagwulonu Richard Chinaza

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

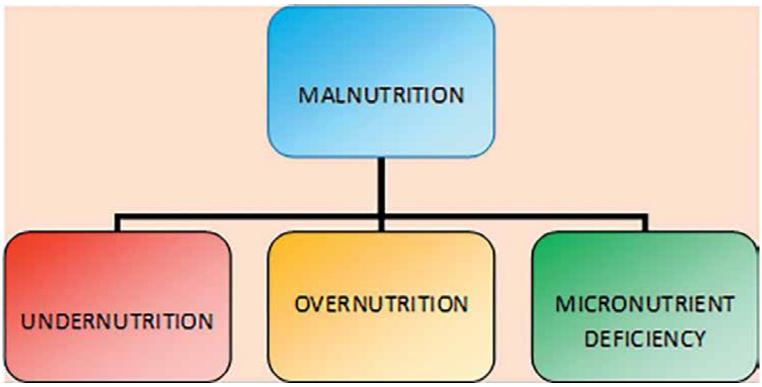

Figure 1.
A figure showing the three burdens of malnutrition.

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

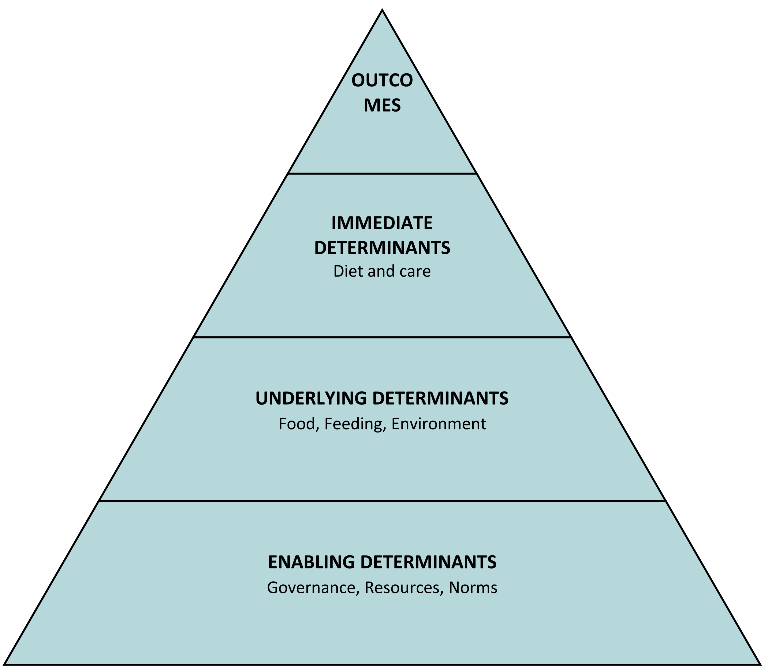

Figure 2.
A pyramid representing the determinants of maternal and child nutrition as adapted and modified from the conceptual framework of UNICEF. The pyramid's base is the most crucial determinant factor (base factor), and it greatly influences what happens to the other parts of the pyramid leading up to the outcome. Governance perhaps explains why we have more malnourished children in Africa and South Asia compared with western Europe.

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 tripple 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 ($\leq$ 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$\geq$ 30, while overweight is $\geq$ 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 deviation 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 consumption 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 challenges, obese children face, such as breathing difficulties, hypertension, cardiovascular 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 development. 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 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 breastfeeding 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 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 is160–950 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-TPP). Research has shown that missense mutations of some arginine residues at the surface of the α-TPP 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-TPP, but this activity is lost with an arginine mutant α-TPP [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

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

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

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**).

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 predisposal 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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Malnutrition is the specific condition produced by the intake of too few macronutrients, too many macronutrients (obesity), or inordinate amounts of inappropriate substances such as alcohol. Globally, malnutrition is a major nutritional disorder, especially in developing economies. Poor dietary habits and imbalanced nutrient intake result in adverse consequences on normal body functionality. This book highlights the major causes of malnutrition and how to overcome this problem. Chapters address such topics as energy metabolism and balance, diagnosis of malnutrition, negative effects of malnutrition, sugar and its impact on health, malnutrition in the elderly and children, and much more.

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