NUTRITION IN MEDICINE: MICRONUTRIENTS

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ABSTRACT

Micronutrients, comprising essential vitamins and minerals, play a pivotal role in sustaining physiological functions, promoting growth, and preventing chronic diseases. Despite their necessity in trace amounts, deficiencies in micronutrients termed as "hidden hunger" affect over two billion people globally, posing a significant public health burden. This comprehensive review explores the biochemical, clinical, dietary, and functional assessment of micronutrient status while highlighting the most common deficiencies, including iron, vitamin A, folate, iodine, vitamin D, and calcium.

Populations at heightened risk include pregnant women, children, and the elderly, with micronutrient deficiencies contributing to impaired immunity, cognitive dysfunction, poor bone health, and increased susceptibility to infectious and chronic diseases. Factors influencing micronutrient requirements such as age, sex, physical activity, and health conditions are critically examined alongside global dietary inadequacies.

The article emphasizes assessment techniques like biomarker analysis, food frequency questionnaires, and functional testing, along with interventions such as dietary modifications, supplementation strategies, public health initiatives, and food fortification. It also investigates emerging research areas, including the role of the gut microbiome, genetic predispositions, and personalized nutrition approaches.

The synergistic and antagonistic interactions between micronutrients and their modulation by drugs and dietary patterns are discussed to underline the complexity of achieving optimal micronutrient balance. Future directions emphasize integrating nutrigenomics and advanced bio-profiling to develop tailored nutritional recommendations. Conclusively, addressing micronutrient deficiencies demands a multi-sectoral, evidence-based approach encompassing education, policy reforms, and innovation in dietary strategies to ensure better health outcomes across populations.

KEYWORDS: Micronutrients, Nutrient Deficiency, Hidden Hunger, Nutritional Assessment, Dietary Intake, Biomarkers, Iron Deficiency, Vitamin D, Supplementation, Public Health Nutrition, Chronic Diseases, Personalized Nutrition, Nutrigenomics, Gut Microbiome, Food Fortification

1. INTRODUCTION TO MICRONUTRIENTS

Micronutrients define all essential vitamins and minerals necessary for a number of vital functions. Vitamins are organic compounds functioning in a co-enzyme manner, while minerals are inorganic elements acting mainly as cofactors. The body cannot synthesize them in sufficient amount, so daily intake is required through diet. A lack of micronutrients may result in severe health disorders, currently considered major risk factors for chronic diseases 1. Micronutrient deficiencies (MNDs) have a substantial impact on health, development, and well-being, being a common condition globally, affecting about two billion people today. This is not a problem of developing countries exclusively; many in Western societies are routinely diagnosed with MNDs too. Generally, this is like an iceberg. Though the health problems caused by MNDs are well known, the "nutritional" part of the problem needs more attention. Malnutrition is the major cause of the development of MNDs, which includes low intake or malabsorption of a variety of micronutrients. Pregnant women, children under five years, and elderly people have different needs for micronutrients and tend to be more likely to suffer from MNDs. Thus, it is suggested that the risk assessment of these groups of populations be prioritized 2. The most frequent deficiency is iron, followed by vitamin A, folate, iodine, and zinc. Healthy status and MNDs can be evaluated from various aspects with some widely used methods, like qualitative questionnaires, quantitive food frequency questionnaire, biochemical, clinical, or anthropometric measurements. The most direct and accurate analysis of MNDs uses biological samples to detect the concentrations of metabolites, namely, metabolite biomarkers. A variety of techniques can be employed, including mass spectrometry, enzyme-linked immunosorbent assay, electrochemical biosensors, and chemiluminescence immunoassay.

2. ASSESSMENT OF MICRONUTRIENT STATUS

Since nutrition is an essential factor in the prevention and management of noncommunicable diseases (NCDs), the improvement of nutrition among practitioners is a major priority to comprehensively deploy such tasks. Health professionals are an important

target group for nutrition training since good knowledge, awareness, and practices on nutrition and ongoing healthy eating habits among them are associated with better public outreach and effectiveness of activities regarding sustainable change of behaviors related to diet among populations. However, most medical schools focus on nutrition insufficiently. Therefore, the aim of this study was to assess KAP in nutrition among professionals and students in the medical fields in Hungary with special emphasis on their education and training history.

There is a significant difference in KAP between medical students and health care professionals. On average, health care professionals have better KAP scores than students. Thoughtful education in a field of nutrition correlates with better KAP. With regard to professional dimensions of KAP, students acquired lower P scores than professionals, while there was no difference between the two groups in pre-professional dimensions. Regarding special training in nutrition, a moderate improvement of KAP was found. However, the overall impression is not favorable since the questions referring to the knowledge of hazards of dietary habits point out that the participants' everyday nutrition is poor, which is alarming since these determinants of nutrition are the most relevant ones.

Knowing their KAP regarding nutrition could be very useful for health care professionals, since they are significant opinion leaders in this area and they can serve as role models for their patients. Thus, appropriate education and training for these factors would lead to sustained improvements in dietary habits, and consequently in health. Apart from work, health care professionals should also accept special training courses in nutrition. In Hungary, providing training during existing courses, via e-learning platforms or as obligatory regular further training would be options to achieve this goal.

2.1. Biochemical Assessment

Nutritional deficiencies can develop insidiously and have the potential to progressively result in symptoms that are subtle and ambiguous 3. Consequently, diagnostic methodologies and micronutrient supplementation involving multiple components are frequently ineffective, as both acute and chronic disease phases are generally rejected. Biochemical assessment is required either to confirm subclinical deficiency or nutritional electronic prescriptions for cost-effective prevention of disease progression and treatment. Biomarkers of Nutrition and Health are analytical determinants that can objectively and accurately quantify nutritional status 4. Such benchmarks are further useful to screen general population micronutrient deficiencies, which finally bid for preventing chronic disease and enhancing health.

Chemical assessment for the specific and accurate prescription of a diet with all appropriate micronutrients is now possible through nutritional biomarkers. A biomarker can be defined as a characteristic that has been objectively measured and evaluated as an indicator of biological process status. A nutritional biomarker can measure characteristics that objectively and accurately quantitatively represent nutrition status with respect to either nutrient intake or metabolism. Biomarkers can be part of biological samples obtained via biological mechanisms that assess micronutrient concentration or status within the body. Micronutrient deficiencies diagnosed biochemically through blood and urine means of assessment and either exclusion or addition of supplements are plentiful in practice. Micronutrients are a diverse group of chemicals whose status can be extracted from a mineral or vitamin consumption crude fraction such as food products, blood, urine, or hair.

2.2. Clinical Assessment

The nutrition assessment process is based on the four domains of the Nutrition Care Process (NCP): nutritional screening/assessment, diagnosis, intervention, and monitoring/evaluation. This article will focus on nutritional screening and assessment. Nutritional screening evaluates the likelihood of vulnerability to malnutrition, considering a limited number of criteria. Nutritional status assessment includes a comprehensive evaluation of anthropometric, biochemical, clinical, dietary,

economic, environmental, and psychological factors. Newly admitted patients, outpatients, and patients on elective procedures must undergo routine nutritional screening. The screening must be performed within 24 hours of admission, preferably on the day of admission or earlier. Appropriate follow-up must be instituted, while nutritional assessment must be performed within 7 days of admission, or at least before surgery in the perioperative setting.

The nutritional routing screening procedure includes a general part comprising three questions designed to identify three areas of possible malnutrition, namely recent weight loss, low dietary intake, and the presence of any disease causing increased nutritional risk. Poor compliance with nutrition assessment is often due to misconceptions regarding its complexity. However, many valid instruments can be administered by healthcare professionals other than dietitians. An ideal tool should be readily available, brief, simple to use, easy to score, reliable, valid, sensitive, specific, practical, reproducible across different patient populations, and available in different languages. Along with healthcare resources, laboratory costs and time required to perform techniques should also be considered. Nutritional screening: malnutrition risk screening (the first level of detection of malnutrition). It is recommended within the first 24 hours following disease/hospitalization events in all healthcare settings. The aim of screening instruments is not to describe the degree of malnutrition, but rather to identify individuals who may be malnourished or at risk of developing malnutrition.

2.3. Dietary Assessment

Dietary assessment aims to quantify food consumption to characterize an individual or population's diet. It estimates nutrient intake, examine relationships with health outcomes, and guide improvements. There are multiple methods to assess dietary intake reflecting food and nutrient databases, strength and weaknesses, and investigator experience. Dietary assessment methods can be classified as direct or indirect. The former includes 24-h recalls, food records/diaries, weighed food records, and direct observation. All are considered 'gold standard' methods or reference measures and valid for assessing usual food consumption. Indirect methods include food frequency questionnaires (FFQs), screeners, and health and longevity questions, developed as more practical approaches to dietary assessment for large epidemiological studies. Analyses of national dietary survey data demonstrated that FFQs could estimate food consumption. A novel FFQ was developed to assess food consumption in a population with foods characteristic of a traditional middle eastern diet 3.

Dietary assessment techniques have the challenge of capturing the seasonal, episodic, and infrequent consumption of foods typical in a traditional population. A systematic review used EpiChronic as an additional tool to assist in dietary assessment analysis. 24-h recall is often considered 'gold standard', but there are no perfect methods as hallucination bias exists in all methods. Weighting food records (wFR) is necessary for the successful application of data-driven comparison methods, and further efforts should be undertaken to develop non-linear evaluation methods. The 3-point HM/2 questions had high agreement with the 24-h dietary recalls in a modal diet. Data-driven methods however need the absolute values of the dietary assessment results to ensure the practical value of the comparison methods.

2.4. Functional Assessment

Human beings are known to require a multitude of carcinogenic, cytostatic, viral, and other challenging agents to elicit a balance between normal development and disruption of basic processes. In an environment with constant nutrient deprivation, organ loss, and blindly mutagenized transcriptomes, normal development still seems possible. Even in absence of a directly functional p53 protein or functional cyclin-dependent kinase 1 (cdc2) pathway, an extraordinary number of processes interacting with these systems - notably, mitotic catastrophe - still produce a degree of normality. Despite a general inability to probe deeper into recognized mutational targets, such as the ras or p53 genes, archaeal-like telomere-addition-like mechanisms and chimeric replication origins can quickly restore more benign differentiation paths. Thus

normality seems more robust than might be expected. However, despite this robustness, the earliest developing organs take on very specific cellular structures from which normality escapes into tumors with abnormal, but consistent structural phenotypes. Normality then survives longer through the targeting of the alternative pathways operating within growing cancer cells than through the targeting of mutational substrates.

An alternative, functional theory of carcinogenesis is proffered in which societies, ecosystems and economies can also become malignant. The components of normality and tumorigenicity within a human cell fall within the adult stem cell (ASC) and malignantly transformed stem cell categories, respectively. Technology and culture can be situated within the same framework. Tumors, and for that matter malignant societies, ecosystems and economies, exploit disruptive realities in environments which offer favorable opportunities for growth 5. Thus, a malignantly-transformed cell may be viewed as a proliferating constituent of a foreign entity, a locale of infrastructure lacking interspecific, Toll-like recognition. At the same time, malignantly-transformed cells may also be viewed as exploitative outsiders proliferating in a highly narrowed ecosystem, an industry and society which lacks inputs in the form of innovation, alternatives, and development.

It seems probable that any line of thought characterizing one scale must also characterize them all. The advent of an alternative concept of malignancy - predatory resource depletion, ecological regime shift, decline and collapse with exit to a low-dimensional attractor - runs parallel to the development of this paradigm in the biological sciences. Malignant outsidership may be induced to yield both "killing trials" and early intervention schemes. The concept of a hierarchy with initial normality and malignancy blooms may usefully frame past and current investigations into the generation of cells, ecosystems, and societies of query. In the case of cells, how do an initial population of ASC-like normal cells undergo mutation and selection so as to assume the appearance and operation of a heterocellular, tumigenic structure? The success of metabolic collapse of cancer development and progression targeted therapies is questioned 6.

3. MICRONUTRIENT REQUIREMENTS

Micronutrients, vitamins and trace elements are indispensable constituents of the human diet, being essential for a variety of vital functions, such as DNA synthesis, transcription and repair, translation, neurotransmitter synthesis, signal transduction, gene transcription, hormonal actions, etc. They are also necessary to combat oxidative stress, during which reactive oxygen species attack biomolecules, giving rise to chain reactions leading to cell death. Old and new meta-analytic data confirm that the prevalence and severity of micronutrient deficiencies is a global problem, concerning about two billion people, primarily in developing countries. However, in most cases, deficiencies are treatable with diet enrichment and/or dietary supplementation of the elements in lack 1. Drug-nutrient interactions can also lead to alteration of the bioavailability of the micronutrient reducing or depleting it. Oftentimes, both reduced intake and malabsorption come to play simultaneously, implementing a vicious circle. Long-term fortification programs for at-risk populations can prevent and restore deficiencies. Preservation of elemental homeostasis is guaranteed by a complex regulatory system, which modulates food absorption and transfer from reserves when necessary. The analysis of bio-molecular recognition events concerning micronutrient uptake, transfer and metabolism request efficient hydrophilic and hydrophobic model system to remain in the nanometer size. The formulation of the pre-clinical and clinical preparation is of key importance. Accurate knowledge of the physico-chemical properties of the preparation and the conditions used for the in vivo delivery procedure is also crucial information for the job 7.

3.1. Recommended Dietary Allowances (RDAs)

There is little ground for optimism regarding the fraction of the healthiest diets that achieve the barely adequate levels recommended by nutritionists, let alone the higher levels that would help to promote optimal nutrition and prevent some chronic diseases. In fact,

with research on , and with modern analytical methods, there are reasons to believe that there are many more inadequate diets than is generally suspected. Early in the information vacuum regarding nutritional sufficiency for health care, RDA-like reference values began to be adopted worldwide by several governments and regulatory agencies, in recognition of mounting evidence that Vitamins A, D, C, E, B6, B12, Folic Acid, Calcium, Iron, Copper, Zinc, Selenium and Iodine can directly or indirectly (via mood) influence health. Governments established RDA-like Reference Daily Intake guidelines (RDI) for many of these vitamins and minerals. Other governments established similar guidelines for varying fractions.

It is important to clarify that comparison of Reference Daily Intake guidelines with diet data, and the actual amounts consumed or ingested in supplemented form is complicated. The RDA developed for the USA is a benchmark utilizing a median daily intake (MDI) as a 100% bar. Due to inter- and intra population differences, the amount needed may vary considerably, and it is best practice to conduct a sensitivity analysis considering lower and upper bounds of assumed intake and standard deviation. The goal of the current study is to investigate the adequacy of whole food diets and individual food supplements as sources of micronutrients for the calculation of the proportion of sufficiency against official reference values (RDA, AI and UL) 8.

3.2. Tolerable Upper Intake Levels (ULs)

Excessive intakes of vitamins and minerals can result in adverse health effects other than those diseases that occur due to insufficient intakes. In order to evaluate and manage potential excessive micronutrient intake, several (inter)national committees have set tolerable upper intake levels (ULs) for some vitamins and minerals. The UL is the maximum level of total chronic daily intake of a nutrient judged to be unlikely to pose a risk of adverse health effects to almost all individuals in the general population. 'Tolerable' means physiologically tolerable by humans. The UL is not a recommended level of intake but is an estimate of the highest level of habitual intake of a nutrient that carries no appreciable risk of adverse health effects. Therefore, it cannot be stated that the proportion of the population with micronutrient intakes above the UL has too high intakes; however, they are potentially at risk of adverse health effects 9. Micronutrient intake is defined as the amount of each vitamin and mineral consumed. Different from foreign compounds, micronutrients are subject to homeostatic control whereby the body content of a micronutrient is regulated over a range of intake, thereby – at least to some level – preventing a deficiency state and excessive body retention and toxicity. However, this homeostatic control process is not perfect. Adjustment of the dietary recommendation to a increasing requirement can be too late and it may also be unable to compensate for a high intake of a bioactive form of a vitamin that could result in permanent adverse health effects by overwhelming the homeostatic control mechanism. For these reasons, it is important to assess whether the usual intake of vitamins and minerals in a general healthy population is too low or too high. The threshold in dietary intake below which an adverse health effect may occur is called an acceptable or tolerable lower intake level, and the threshold above which an adverse health effect may occur is called a UL.

3.3. Factors Influencing Requirements

Inadequate micronutrient intake is common worldwide, with risk groups identified including elderly individuals, pregnant women, vegans, and some endurance athletes. Adapting intake to energy expenditure while accounting for changes in food choices due to higher expenditure could prevent low micronutrient intake. Energy turnover is among the factors influencing micronutrient requirements, alongside sex, age, and health conditions 10. Current estimates of micronutrient requirements may not account for energy expenditure, with the derivation of nutrient allowances largely based on studies involving physically inactive persons. For persons engaging in increased levels of physical activity, mathematical adjustments may be necessary to account for lower micronutrient and macronutrient intake among persons with high activity levels and a propensity to lose weight.

Adequate intake of vitamin A, vitamin C, and vitamin B group was in line with other reports, while the

percentage of individuals meeting intake guidelines for vitamin D, vitamin E, and vitamin B9 was low 7. Mean intake of minerals and trace elements demonstrated that iron, magnesium, and selenium were adequate for most of the sample, while sodium, potassium, and calcium intake were relatively low. This study assessed dietary intake of vitamins and minerals in a sample of 1838 adults and older adults randomly recruited in Catania, southeastern Italy, separately by age and sex, adherence to guidelines, food sources, and other relevant factors. As a secondary aim, this study contributed to describing variability by participants' age and sex to provide risk estimates of inadequate intake. Micronuts and minerals are crucial compounds for the proper functioning of metabolic enzymes and regulation of gene transcription. Most of the participants had a proper intake of wide-range vitamins and mineral intake.

4. COMMON MICRONUTRIENT DEFICIENCIES

Micronutrients are needed in small amounts, but they are vital for the body's function. They supply a foundation for enzyme reactions and are required for the action and synthesis of hormones necessary for metabolic processes. Micronutrient deficiency is the most widespread form of under-nutrition in the world. It affects infants, children, adolescent girls, and women of reproductive age. An estimated 2 billion people suffer from a deficiency in iodine, iron, folic acid, or vitamin A. Such deficiencies cause irreversible harm in children and fetal life. Moreover, epidemiological studies have associated the deficiency of micronutrients with an increased risk of infections, autoimmunity, cancers, chronic diseases, and poor bone mineralization. Recent studies have also suggested that low vitamin D may be linked to human insulin resistance.

Almost a quarter of the global population suffers from vitamin D deficiency. Low serum vitamin D levels also accompany obesity and metabolic syndrome, especially insulin resistance and type 2 diabetes. Low serum vitamin D and adipokine imbalance may preclude the development of insulin resistance and subsequent diabetes. Increased parathyroid hormone secretion in response to vitamin D deficiency is also associated with decreased insulin sensitivity and the development of metabolic syndrome and type 2 diabetes. Vitamin

D depletion has also been shown to impair pancreatic beta cell function and to decrease the release of insulin into the serum in humans.

Sufficient vitamin D is essential to avoid poor health throughout the life cycle, given the evidence for long-term effects. The early origins of poor health in adulthood may occur through fetal programming via maternal risk factors, such as overweight. Poor pregnancy nutrition in both macro and micro-nutrients, such as folic acid, iron, vitamin D, and vitamin A, is associated with higher risks of obstetric risks and pregnancy-related diabetes. Short gestation length, preterm birth, small for gestational age, poor fetal growth, and homocysteine metabolism can play an intermediate role in this complex relationship between maternal overweight and femoral length growth.

Micronutrient deficiencies are widespread during the first two years of life. Worldwide, it is estimated that 45% of children under five years old suffer from iron deficiency almost equal in prevalence between developed and developing countries. Children are at increased risk of vitamin A deficiency due to the depletion of maternal stores during breastfeeding. A mother who herself suffers from a vitamin A deficiency is unlikely to be able to store sufficient amounts in her offspring liver. Studies have found that 1 in 5 children age 1-11 years are vitamin D deficient. Moreover, older children aged 6-11 were at greater risk of deficiency compared to younger children in a study conducted in several developing countries.

4.1. Vitamin A Deficiency

Vitamin A is important for many bodily functions, including vision, growth, differentiation, reproduction, and immunity. It produces three retinoids (retinol, retinal, and retinoic acid) that maintain cell homeostasis, enable reproduction, formation of mucosal barriers, and control gene expressions. Vitamin A deficiency (VAD) is still a public health issue affecting 250 million children <5 years in Resource Poor settings, blindness, and premature death Each year VAD is estimated to result in 500,000 children with xerophthalmia leading to blindness 11. 3-4 million

children die each year mainly from infections. Failures of early linear growth and malnutrition are against measurement of VAD through under-weight, stunting, and wasting. Most childhood blindness globally occurs in poor settings where prevalence of confluent measles and VAD are high. Prevalence of VAD is most critical at the highest mortality rates.

Vitamin A deficiency (VAD) in the context of primary poor intakes of vitamin A, dark green leafy vegetables non-provitamin A carotenoids, poor liver storage, illegal hunting of migratory birds, and burning of forests containing species-rich environments. A retinol binding protein (RBP) test-based VAD tracking study to identify snags and consumer information inputs. Assessment strategies include cross-sectional surveys, repeated surveys, rapid assessment, monitoring and surveillance. Knowledge of the schooling impact of the study to enhance the primary school health program 12. The AAA estimates grain supply and demand at the global, regional, and country levels using a combination of equilibrium models for some products and simple demand/supply models for others. The base model contains equations/descriptions for supply, demand, stocks, trade, and prices for the crops in question.

4.2. Iron Deficiency

Iron deficiency and iron deficiency anemia are significant public health issues, especially in vulnerable populations. Globally, it is estimated that 1.5 billion people suffer from anaemia. Of these, almost half are attributable to iron deficiency. Iron deficiency is especially problematic for children and vegetarians, who often do not consume adequate dietary iron. Schools can play a role in improving the consumption of iron and iron-rich foods. Iron deficiency is more prevalent in premenopausal women than men. However, developmental effects of iron deficiency on fetal and neonatal brains may compromise neurocognitive function later in life. The vulnerability of certain populations for their development warrants lifestyle intervention to improve iron status and mitigate iron deficiency-product interactions. Iron repletion is the cornerstone of treatment strategies. Normalizing iron deficiency forces a re-evaluation of the 13. However, the biokinetics and clinical application of iron supplementation products can differ widely. Dietary and therapeutic options, either administrated with or without vitamin C, can be considered to improve the acceptance of medical therapy.

4.3. Vitamin D Deficiency

Vitamin D is a fat-soluble vitamin that is important for good health. It may take the form of either vitamin D2 or vitamin D3. Vitamin D2 is formed by ultraviolet irradiation of ergosterol; Vitamin D3 is formed by ultraviolet irradiation of 7-dehydrocholesterol in the skin and is the biologically active form in humans. In humans, vitamin D is ingested via diet and is synthesized in the skin upon exposure to UVB radiation, summit midday sun strength, elevation, and latitude effects. Vitamin D is activated by hydroxylation initially in the liver, by 25-hydroxylase, to produce 25-hydroxyvitamin D (25[OH]D). 25(OH)D is transported to the kidney, where a second hydroxylation occurs by 1α-hydroxylase to produce calcitriol (1,25[OH]2D), which regulates calcium and phosphorous homeostasis. Skeletal muscle also has ability to synthesize vitamin D, which seems to fall more on a paracrine regulatory role of calcitriol and perhaps other unidentified vitamin D metabolites 14.

Sunshine is the best source of vitamin D. After absorption, skin provides as much as 90% of body's vitamin D requirement, prompting the liver and kidney to activate circulating pro-vitamins into active vitamin D. Food sources of vitamin D are fortified dairy products, fish oils, livers, and egg yolk. A small amount is contributed by meat, milk, cereals, and mushrooms when calcified. The five-fold rise in childhood rickets seen since the late 1980s has been attributed to the decrease in midday sun exposure. Its eventide association with respiratory problem indicators across North America raises further concern about vitamin D deficiency states across the continent.

Dark-skinned folk, who have 94% to 98% of parients, are challenged by endemic hypovitaminosis D in the northern ruins. Factors effecting vitamin D receptor consumption and action need epitomizing. Human gender differentially regulates the vitamin D receptor, which may increase the risk for poorer outcomes. Auto-

immunization, base pair mismatches, and signal alterations affect circulating pro-vitamin and its receptors. A formidable genetic climate currently shields man from receptor upregulation. Polymorphism Kir6.1 A>G respects a phenomenon under bewilderness. Up to 191 disparate receptor site mutational substitutions have been described in vitamin D dependent conditions.

4.4. Folate Deficiency

Folic acid (Vitamin B9, folate) participates in many metabolic processes as a carrier of 1-carbon units in the biosynthesis of nucleotides and remethylation of homocysteine. Folate was first isolated by Yarrowia lipolytica yeast in 1941 from spinach. It is a pyrimidine derivative (pteridine) with 1-pteroylglutamic acid. Reduced monoglutamyl derivative 5-methyl-tetrahydro folate (5MTHF) is actively transported into cells by special folate transporters from the SLC family and is converted into other tetrahydro folate coenzymes (THF, 5- and 10-formyl-THF, 5,10-methenyl-THF). A deficiency of folate can disrupt purine and pyrimidine synthesis, causing the accumulation of S-adenosylhomocysteine and homocysteine. Folate deficiency is related to genetic disorders, malnutrition, and malabsorption 15.

Folate deficiency is estimated to be the most prevalent vitamin deficiency in the world. It is seen in up to 10% of the USA population. Their average diet folate intake is 237 μg, which is below the estimated average requirement of 320 μg. Folate deficiency (<4.4 nmol/L) ~2% in USA and ~39% among Mexicans. Folate status is measured by serum or red blood cell folate concentration. In older adults, RBC folate remains normal with serum folate deficiency. Folate deficiency and associated metabolic disorders are particularly concerning for the elderly and women of reproductive age who follow strict diets and rely on micronutrient-reduced foods and medications.

Newborns have folate deficiency even with folate supplementation prior to delivery. Maternal Vitamin B12 (cobalamin) deficiency causes megaloblastic anemia in both mothers and newborns. The strength of the association between vitamin B12 deficiency and hyperhomocysteinemia increased when combined with low folate. Maternal serum cobalamin concentrations among Puerto Rican drug-using women remained high >2 mos postpartum reduced risk of poor infant cognitive outcomes at 4–5 y of age. In older adult populations, impaired cognitive function is associated with low plasma total homocysteine, low folate, and low Vitamin B12. Folate may be the most active in reducing risk prior to dementia diagnosis. Low active B12 increased the risk of new-onset CR (converters) to dementia and cognitive decline among eligible Non-Convertors.

4.5. Calcium Deficiency

Calcium deficiency remains a public health issue in both developed and developing countries. Populations deficient in calcium include a broad array of individuals who have various degrees of dairy product restrictions, such as those of Asian or Native North American descent, and whom are low consumers of calcium-rich foods. The moves toward non-dairy-based diets, particularly in adolescent females for weight management, and the move toward fat-reduced dietary practices among pre- and post-menopausal women have contributed to the prevalence of low calcium intake. Biochemical and biological data demonstrate that an unsuspected group, premenopausal women from the Southern USA, may be at high risk of calcium deficiency. Adolescence is a period of intense bone formation 16. Factors including lack of knowledge about healthy practices, focusing on body image and weight loss, familial attitudes, and peer pressure contribute to women's dietary lifestyles. Due to this, pre-menopausal females are at high risk of calcium deficiency through food restrictions.

Women are also at risk of calcium deficiency during transitions in the life cycle. After menopause, women find themselves having inflammatory bone loss due to hormonal changes. Calcium losses following menopause can reach as high as 10% within the first five years. As with many of the previously mentioned risk factors, hormone replacement therapy is an effective means of attenuating bone loss. As with adolescent habit changes and the elderly habit considerations, avoidance

of these changes or drastic inclusion of calcium supplementation may better control for calcium deficiency. A cohort of post-menopausal women vending established histories of low calcium intakes and chronic disease after collecting appropriate consumer activities' tools would have a large number of participants.

Colloquies, interviews, and surveys describing calcium intakes and consumer activity patterns in detail would be included. The research area on health aspects is not new or novel; however, little attention has been given to the groups most at risk of developing the affliction. Due to that, a unique point of investigations concerning calcium deficiency will be provided. Obtaining at-risk individuals is an essential first step in better comprehending how those individuals interpret events and practices; of more importance, these individuals possess the means to improve public and health policy.

5. HEALTH IMPLICATIONS OF DEFICIENCIES

Micronutrient deficiencies affect nearly 2 billion people in the world 17. The most common elements deficient in the diet worldwide include vitamin A, vitamin D, vitamin B12, vitamin C, calcium, folate, iron, and zinc. The most widespread deficiency globally is iron deficiency and its corresponding anemia. Prevalence estimates of this are over 800 million people, most of which are premenopausal women and children. Deficiency of folate is next with around 300 million people estimated to not be consuming enough of it due to a lack of green leafy vegetables in their diet. 2 billion people are estimated to be at risk of inadequate intake of vitamin A. Deficiencies of calcium, vitamin B12, and vitamin D are also estimated to affect millions of people.

Deficiencies of micronutrients can lead to disease states, however, it may take a longer time for the symptoms to manifest as compared to with macronutrient deficiencies. Deficient subjects might seem to be healthy and even thriving. After having followed a pathological sequence, the initial performance drop will be exacerbated as the deficiency continues, leading to clinical symptoms.

Despite sufficient or even excessive caloric intake, energy-rich but nutrient-poor diets can lead to hidden hunger, wherein micronutrient inadequacies ultimately cause body system malfunction. Hidden hunger is a condition characterized by the inadequacies of vitamins and minerals whereas hunger is a deficiency of macronutrients. The latter usually leads to apparent health issues and may elicit immediate attention from the medical community and authorities. The widely adopted term hidden hunger describes the situation where marginal micronutrient deficiencies which do not provoke apparent health problems but may cause very harmful effects on health.

5.1. Impact on Immune Function

A wide array of micro- and macronutrients is vital for normal immune system development and functioning, which include minerals like copper, manganese, iodine, iron and zinc, vitamins such as C, D, E, A and B-vitamins as well as essential fatty acids (EFA) 18. Optimizing intake of these nutrients is particularly important not only in the treatment of chronic conditions such as cancer and other malignancies, chronic inflammatory and allergic disease but also in modifying the risk of viral infections including cold, influenza and COVID-19. Vitamin D, omega-3 fatty acids, zinc and vitamins A and E have all been suggested as potentially modifying susceptibility to infection or the severity and progression of disease. The human immune system exhibits remarkable plasticity in its response to environmental factors. In particular, it can adapt to high antigenic load and inflammatory patterns, as observed in chronic infectious disease and cancer, yet with negative consequences. It can also actively down-modulate potentially injurious inflammation and revert to a more regulatory phenotype in relation to physical exercise, caloric restriction, or the use of drugs or certain dietary habits. Human history provides examples of the former kind, while healthier longevity in certain human populations is attributable to progressive down-modulation. A wide array of immune-triggering factors can often lift the immune response off its usual homeostatic level, and manipulation of numerous exogenous factors can exert effects on the immune response. Micronutrients exert a wide variety of functions during the immune response, and their

deficiency could lead to dysregulation of the immune system. Vitamin C is critical for proper L-arginine utilization, which is necessary for TNF-α and nitric oxide production, and vitamin C deficiency could jeopardize NO production, which would prevent Th1 cell differentiation. A shredded margin of T cells, and follicular helper T cells could be found after vitamin C intake, suggesting the cellular immune function could be enhanced with higher levels of vitamin C. Deficiency of vitamin D leads to increased susceptibility to infection and is associated with the progression of chronic disease. However, daily vitamin D supplementation has yet to be established due to a lack of consensus on its prolonged mechanism. Hypervitaminosis E could inhibit the activity of T cells, cytotoxic T lymphocyte and NK cells and thus are unfavorable conditions in the viral infection. Sufficient dietary zinc intake can enhance T cell immune function by promoting immune memory and effector polarization by altering T cell metabolic programming 19. Zinc deficiency could induce intracellular aberrations in these processes through dysregulating key enzymes, impairing IL-12 and IFN secretion from DCs and subsequently influencing Th1 differentiation. Iron storage might be recruited in order to inhibit dendritic cell maturation in an inflammatory microenvironment. Iron deficiency could inhibit CD4+T+/CD8+T+ activation and polarization during the immune response, while iron overload could induce TGF-β gene expression and promote T regulatory cells

5.2. Impact on Bone Health

Osteoporosis is a major health problem, as it leads to low-bone-mineral density (BMD) and microarchitectural deterioration of bone tissue, greatly increasing the risk of fractures 20. It is a silent disease until it is too late and fracture occurs, at which point it is too late to prevent. The treatment of osteoporosis requires a multi-faceted approach, including dietary, biochemical, physiological, exercise physiology, mechanical, and hormonal influences.

Methods to satisfactorily quantify are a somewhat modern development for a disease that has probably existed since humans first became bipedal. Bone mass may not be easily and systematically measured until recently. Since then the diagnostic tools have been refined to be non-invasive, compact, and relatively cheap. These techniques are now world-wide qualitative instruments, a fact not lost in modern medicine. There exist well-structured whole food methods to curb osteoporosis risk factors, if sufficiently utilised. However, the need to now be more pro-active toward nutritional information systems through publicly funded websites, journals, and television/media is clear. Ageing societies require widespread nutritional help and professional nutritional information systems would partly fulfil this long-neglected need.

The seminal work of Drs. C.E. Turner and A.R. Houghton in the mid-1990s showed the availability of the "anti-osteoporotic" whole foods before the consumer fast-food epidemic and the complex "unproven" food/nutritional supplements that were subsequently marketed. The roles and inter-relationships of minerals, vitamins, protein, and other food components in bone health were established pre-2000. Isolated micronutrient supplementation is inherently flawed and not a legitimate intervention for osteoporosis prevention, as it does not operate within the complex biological milieu of whole foods, which can each include thousands of known present components plus many more continually evolving larger molecules. Some minerals function in a whole food setting, indirectly altering intestinal milieu and/or availability. Other components can favourably alter protein or lipid function. Inter-component synergies are also required for efficacious influences on bone health.

5.3. Impact on Cognitive Function

Preservation of cognitive ability into older age is a growing concern for the population. A far greater concern is the prevalence of cognitive impairment. Recent studies estimate that between 10–25% of older populations are cognitively impaired, with rates increasing every year. This presents a significant problem to aging adults, families, and the healthcare system in general. Maintaining good health is important throughout the lifespan, but preserving cognition in older age is especially significant as this will result in a

longer healthy life for older adults. There are a multitude of factors that can affect cognition, but examine the role that nutrition plays on cognitive health.

Micronutrients, composed of vitamins and minerals, are critical for various cellular function, modulating energy metabolism, synaptic transmission, and even cognition. It is hypothesized that a deficiency in one or more nutrients will affect cognitive health, manifested by a decline in cognition over time. Nutritional deficiency is common in older adults, and it is thought that this may contribute to cognitive impairment. Impaired appetite with age, combined with a reduced dietary calorie intake, can result in malnutrition. In addition, reduced nutrition education may fail to address nutrient density, and as a result, deficiencies become common 21. However, micronutrient status in older adults has received limited empirical, theoretical, and philosophical attention. The micronutrients discussed include vitamin D, various antioxidants, and omega-3 fatty acids.

One nutritional deficiency that is common in older adults is a lack of vitamin D, which is primarily produced through the conversion of 7-dehydrocholesterol to vitamin D after ultraviolet irradiation of the skin. A greater reduction in activation of vitamin D through compromised liver function and reduced kidney activation occurs with age. Older adults with vitamin D levels above 15 ng/mL showed better scores on cognitive tasks compared to those below the deficiency threshold. In addition, correction of vitamin D deficiency in the elderly has immense potential regarding cognitive impairment; older adults provided 800 IU of vitamin D over 18 months showed less cognitive decline due to protective effects against abnormal lateral temporal lobe atrophy.

6. MICRONUTRIENT INTERVENTIONS

Nutritional interventions aimed at alleviating malnutrition must be tailored to the specific needs of the target populations to maximize public health benefit and minimize any potential adverse effects 22. It was emphasized, however, that the group average requirement and safety limit for a micronutrient do not necessarily reflect the adequate or safe intake values for all individuals in that group. The requirement for a micronutrient varies between populations, and within populations it varies by age, gender, life-stage, health condition, use .of medication, genetic profile, which implies that there is also a need for upper intake levels for safety by age and gender group. Such natural variation in requirements leads to a great proportion of a population being at-risk for inadequate micronutrient intake. Chronic disease conditions, such as gastrointestinal disorders, diabetes and cystic fibrosis, or polymorphisms in genetic pathways, may lead to higher requirements for a micronutrient than that assumed in the estimation of the dietary reference values. Complexity in the prevention of public health problems related to micronutrient deficiency was emphasized. Meeting the increased requirement for iron, for instance, is a necessary but will not suffice condition for prevention of iron deficiency; it is necessary as well to exclude any interference between iron and its competitors on the way into the absorption and blood distribution compartments and to exclude inflammation that may diminish iron status. A micronutrient does not necessarily provide benefits in all deficiency conditions. Public health benefits may be profound if iron status is low to moderate, but there may be little or no public health consequences if iron status is adequate or high. Different conditions leading to iron deficiency also may differ in public health consequences; for instance, there was no iron deficiency anemia but the blood lead levels were high enough to impair cognitive development of toddlers. Further, complex interactions may exist between the delivered micronutrients, the micronutrient status of the recipient, digestive function, infestations with agents of infectious diseases or hygiene, use of medications, chemical composition of the diet, and agricultural practices. The interactions between micronutrients include interference in the absorption of iron and zinc and calcium and magnesium, and that copper and iron compete in the intestinal up-take and neurological delivery compartments. Micronutrient–drug interactions have also been documented and can be quite diverse.

6.1. Dietary Modifications

As the world around us evolves, so do our dietary recommendations, which constantly grow more specific, considering culture, traditions, technologies, food processing, production, regulation, and consumer behavior. Such aspects of these recommendations are not universally defined in an exhaustive manner—not even by the World Health Organization (WHO)—besides, such recommendations evolve quickly. Different countries and regions across the world should take them into consideration while performing their own evaluation. Moreover, food groups follow a very diverse systematization, being changed by cultures and traditions, which need to be considered too 23. Therefore, this document will provide recommendations with few normative and static definitions by recommending to explore local dietary guidelines, with cities (or metropolitan areas) as the primary scope for action. On such guidelines, the authors expect the explored cities ensure updated definitions of food groups, healthy recipes in line with the local culture, tradition and seasonality, and foods to limit and habits to avoid, focusing on cultures and traditions that favor overweight at working sites. Upon these cultural and scientific bases, the authors will recommend focusing on food over nutrient levels—defined as countries, cities, or regions of 1,000,000+ inhabitants. The recommendations should aim at sustainable food systems and provide equally light food lists of affordable recipes for unhealthy and healthy foods.

Such food groups and recipes should be reformulated by several different sources in the marketed food system to allow for richer recipes and diets and a wider range of basic and healthy foods. On the nutrition analysis of habits, recipes, and food, they should focus primarily on under-consumed food groups and as secondary targets on over-consumed, disrespected, and imbalanced food groups, with recipes being targeted at dietary staples or traditional home foods. The resulting quantifications should aim at informing potential reduction or advocation of changes at homes. Upon these recommendations, the authors suggest tools to understand dietary habits and grasp updates on recipes daily. The suggested tools and methods should focus on real-time reflection and two-way communication, being cross-platform able to suit different needs (reading levels, languages, age, gender, and occupation). The details on how to perform these recommendations are at the end of this document.

6.2. Supplementation Strategies

Micronutrient supplementation strategies need to be formulated with careful consideration of the supplement dosages in order to be effective, safe, and feasible for long-term use. Formulating dietary supplements with the application of smart technology in food production and for personalized nutrition is the future direction of micronutrient supplementation strategies to meet the challenges of nutrition and health in modern life. The application of smart technology in medical food development, based on rigorous scientific evidence of nutrient molecules and health effects, is the best way to help consumers make educated product selection. In this approach, the strategies of personalized fortification and of co-supplementation with smart food would apply. To enhance adherence and efficacy of micro-nutrient supplementation for chronic diseases, more effort should be made in developing formulated supplements using the smart technology in the food production by bio-probing. Nutritional immunology nutrigenomics using technologies to probe the composition, structure, reactivity, and biological fate of bioactive molecules in diet and food supplement will benefit the meticulous design, development, and standardization of functional foods including medical food 24. The avenues for precious, scalable, and robust food design strategies include in silico design-driven mimicked food matrix reconstruction, in vivo advanced bio-probing targeting microbiota-mediated bioavailability studies, and systems model-based physiological and biological consequence prediction. To spice up the health properties of the isolating target bioactive nutraceuticals, the precision bioprobe/modification/engineering would help - biomimetic device for manufacture of complex's-targeted food matrix, systemic compartment targeting

and pH-mediated release of delivery vehicle, and captive bio-carrier complex on site digestion and absorption. Data-driven intelligent engineering approaches from big data of feeding will regiment the bio-mapping, modelling, and dietary modulation of gut microbiota to elicit the pre-bioactive for drug intervention. Data-driven smart memoration, sensing, and manufacturing food technology would take effect in person-oriented fortification and design of food.

6.3. Public Health Initiatives

At the beginning of this new millennium, health experts particularly focused on preventing the continuing catastrophic and avoidable loss of life among children and pregnant women by offering solutions to prevent infectious diseases in the poorest countries. At-risk groups in LMICs must still receive life-saving vaccines, preventive care, and treatment for these infectious diseases until they become so rare that they can be disrupted by public health initiatives. However, there is less concern to prevent chronic ill-health conditions, debilitation, and the deaths of millions of people, especially children and women of childbearing age, due to subclinical deficiencies of vitamins and minerals (i.e. micronutrients). In LMICs, it is estimated that 142 million children (ages 6-59 months) in non-industrial countries suffer from vitamin A deficiency. This is one of the major contributing factors of the great global burden of disease in 2010 25. Addressing this is but one example of many public health challenges in meeting new and inevitable attempts. It should be noted that meeting the community health needs of individuals suffering diseases attributable to a low intake of vitamins and minerals is best met by population based approaches.

Since the early 1990s, there has been a marked and welcome increase in both awareness and a focused effort to better understand the emergence of increasingly prevalent subclinical micronutrient deficiencies conditions in many LMICs. They receive attention and are being addressed in both high- and middle-income countries. In 1999, the United States Centers for Disease Control and Disease Prevention highlighted ten great public health achievements in an acclaimed series of reports. The public health achievements of water, sanitation, and the control of infectious diseases were emphasized. Little attention was given to health problems affecting developed countries, which remain or are re-emerging in lower income countries, such as micronutrient deficiencies conditions. Micronutrient deficiencies conditions refer to the inadequate or untoward intake or absorption of vitamins and minerals so as to impair normal bodily functions.

Preventing deficiencies in at-risk groups (e.g. women and children) in less developed countries requires the provision (e.g. supplementation) of essential vitamins and minerals. Fortification of basic pillar foods is the only or best strategy for population-based approaches to free at-risk groups and the communities in which they live from diseases attributable to a low intake of vitamins and minerals. The world is following in the ever-widening profit and organizational footsteps of the now bygone epidemic of salt ailing iodine deficiency goiter, rickets and scurvy deficiency. Nutrition-related policies addressing the micronutrient deficiencies in populations among the poor in LMICs begin with control measures like food fortification and behavioural change for the rich and the powerful.

7. ROLE OF MICRONUTRIENTS IN DISEASE PREVENTION

Micronutrients have garnered increasing attention as their roles in health and disease prevention have gradually become more accepted. The concept of specific vitamins and minerals as essential nutrients that prevent disease was largely formulated around the turn of the 20th century, with numerous beneficial compounds already identified by the mid-1940s. Rapid progress in industrial chemistry subsequently enabled the mass production of many vitamins and minerals, culminating in their incorporation into commercial products both as supplements in pharmacies and as food fortificants 1. After decades of widespread, without doubt, ill-advised indiscriminate supplementation and/or fortification, warnings about the realistic threat of overt toxicity began to be issued, especially within the past 30 years. Thinking at this latter time was too late with respect to many important vitamins and minerals. Indeed, long-term and indiscriminate population food

fortification schemes drove some of the most effective drugs to treat or prevent diseases, such as niacin with hyperlipidemia, pyridoxamine with diabetic nephropathy, and calcitriol with hyperparathyroidism 24. Nevertheless, an honest, diligent approach for the scientifically sound use of micronutrients remains, warranting consideration by medical scholars and practitioners. Lipids and macronutrients operate within limited well-defined ranges, failure of which produce averse health outcomes that, in turn, drive the evolution of specific "disease mechanisms." Micronutrients, on the other hand, are generally much less toxic and operate in a more pleiotropic fashion. Furthermore, because of this functional redundancy and alternativeness, both under and over consumption of micronutrients result in subtle but complex perturbations of normal homeostasis before these produce pathologic conditions for which treatment choices decline sharply. Long-term and/or indiscriminate supplementation schemes may drive misallocation of national resources and inequitable health care access, also causing information inertia for continued usage. Such concerns notwithstanding, methods to effectively use micronutrients for the prevention and management of disease are having and will continue to have a profound impact on medicine.

7.1. Chronic Diseases

Nutrition is recognized as an essential component in the prevention of chronic diseases, including periodontal disease. However, the evaluations included in this narrative review present strong evidence to induce a better understanding of how diet, principally the intake of macronutrients and micronutrients, impacts the relationship between nutrition and periodontal diseases. The risk of periodontal diseases increases with 1) high-sugar and high-saturated fat intake, and low-fiber intake, commonly found in the Western diet; and 2) a lack of adherence to healthy dietary indexes. In contrast, the risk of periodontal diseases decreases with 1) low-sugar and high-fiber intake; and 2) strong adherence to healthy dietary indexes. These dietary patterns have been shown to have protective effects against the main chronic diseases of humanity. Among the dietary components, some micronutrients directly and indirectly have a role to prevent periodontal disease, as shown in the present review with specific focus on vitamin A, B, C, calcium, magnesium, zinc, and polyphenols. More specifically, vitamins A, C, and D3, and minerals such as calcium, magnesium, and zinc, are involved in host defenses, bone metabolism, and the integrity of periodontal tissues, whereas antioxidant compounds, such as polyphenols, have effects on the oral microbiota. In addition to these micronutrients, foods or additives could prevent or delay diseases due to their effects on the oral microbiota. Probiotics have beneficial effects on microbiota and overall global health. Milk-based prebiotics could act on the oral microbiota composition with potential health benefits. Hence, nutrition acts as a shared risk factor for both periodontal and chronic diseases, indicating that changes in periodontal health should prompt a focus on dietary quality to reduce the risk of chronic diseases.

7.2. Infectious Diseases

Micronutrients are essential for the optimal function of the immune system. A lack of these nutrients can therefore lead to an increased susceptibility to infectious diseases. A systematic review has shown that in addition to classical macronutrient malnutrition, over 2 billion people worldwide are at risk of micronutrient deficiencies, which are often referred to as hidden hunger 26. Micronutrients have important roles in both the innate and adaptive branches of the immune response. Specifically, vitamins A, B6, B9, B12, C, D, and E, as well as the trace elements iron, copper, zinc, and selenium, have been shown to influence the immune response in several ways. They affect activation, proliferation, and production of immune mediators by innate components such as phagocytes and dendritic cells. Micronutrients can also affect T and B cell activation, differentiation, and antibody production in several ways. Despite this knowledge, data are sparse on the effect of micronutrients on the risk of subsequent infections in humans. Earlier clinical studies performed in the 1990s on healthy children have shown that vitamin A supplementation decreased the risk of respiratory infections and that dietary copper supplementation decreased the risk of diarrhea.

More recently, diverse effects of micronutrient supplementation on the risk of respiratory tract infections and gastroenteritis have been assessed in a clinical study, linking them to circulating micronutrient levels 27. In addition to providing strong evidence on the importance of micronutrients in reducing the risk of infections, these studies also underscore the need to further establish causal relationships between circulating micronutrient levels and the risk of infections. To address this knowledge gap an observational study was performed, from which <1,000 adults in an infectious disease clinic were recruited. Since micronutrient measurements were performed across the cohorts before infection and infection-related hospitalizations, migraine events and blood samples were reassessed. Also, a supplemental dataset with GWA studies performed with individuals of European descent was collected for the MR analysis.

8. MICRONUTRIENT INTERACTIONS

Physical Health | Nutrition in Medicine 23 MICRONUTRIENT INTERACTIONS The simultaneous adequacy of two or more vitamins B1, B2, or B6 is necessary for the normal functioning of their coenzyme forms at the level of the transketolase and pyridoxyl- po4 and/or pyridoxamine-po4 dependent pathways in thiamine, riboflavin, or pyridoxine deficiency. To maintain normal sulphuration and to retain normal sulphydryl levels in the liver tissue, starvation and deficiency of vitamin B6 and sulphur-containing amino acids are required. Serum or tissue zinc co-deficient with pantothenic acid deficiency will cause high copper levels and low concentration of ceruloplasmin, hence low copper and ceruloplasmin levels may be an indication of zinc deficiency. Severe vitamin C deficiency produced by dietary restrictions or a large dose of 6- thiol analogue of ascorbic acid blocks the transport of both the vitamin and its non- degraded analogue towards the intracellular compartments in rats. Collagen synthesis in non-vascular smooth muscle tissues does not depend on vitamin C availability. Prolonged deficiency of B1 has a similar effect on the tropocollagen secreted. As native procollagen molecules are generated, they are rapidly glycosylated by glycosyltransferase, which is inhibited by deficiency of glucose or glucose analogues. Interruption of glycosylation will alter the fibril formation, paving the way for a biochemical basis for brittle bone disease and a possible non-nutritional model for knock-out mutation of glycosyltransferase. Most chronic conditions associated with declining health tend to improve when treated, managed or prevented with micronutrient supplementation. Providing quantitative estimates of micronutrient interactions and predictive models of overall complementary micronutrient use for enhanced health is a necessary step to explore and quantify micronutrient interactions and their contribution to health improvement. The proposed integration method involves conversion of survey-based qualitative data of complementary micronutrient use to quantitative estimates, which can subsequently be used in simplified linear regression and computational modeling to predict overall interactions and health improvement attributable to the use of complementary combinations of micronutrients. Potential micronutrient interactions and sensitive health indicators are quantitatively explored and presented as the first step toward building predictive models of overall health improvement by intersecting multiple complementary micronutrient interactions.

8.1. Synergistic Effects

In essence, investigation of nutrition and disease, their relationship can be analyzed by considering different vitamin-protein interaction networks, both from topological and functional perspective. Given the complex nature of food matrices, their bioavailability with respect to vitamins is heavily dependent on preparation and consumption patterns, and their interactions with other compounds in the diet. Nevertheless, many interactions have been documented, which possess either positive synergistic effects, or antagonistic properties. By focusing on a subset of food-bioactive interactions, cofactor interactions with protein targets were predicted and validated within this approach. The topological network properties of the cofactor-protein interaction networks were computed and compared with previously

determined target networks, and the protein domain distribution across these networks was analyzed. Co-factor binding mutation prediction using evolutionary conservation and biophysical free energy scoring was revealed on the basis of interaction networks obtained through multiple methods 28.

So far, good molecular outlines of the bioactive food mechanisms at the protein level exist, and large networks of food matrices and their effects on protein target networks have been generated. However, given the global changes in dietary consumption patterns, food biomarker-based nutrition and disease analysis becomes of paramount importance for the future. By using a previously obtained food biomarker classification approach based on high-throughput protein activity screening, cofactor-protein interaction predictions and dietary intake mapping were pointed out for six hallmark metabolic and health-related diseases. These results enable the establishment of novel biomarker assays, based on pro- or anti-nutrient food patterns or health states 1.

Trend analysis of dietary intake data showed statistically significant behaviors of tissues and compounds across global food transition phases. A modified GWAS approach incorporating food intake information, dexterity of diets, as well as dietary patterns and consumption behaviors was also provided. Systems understanding of nutrition and health, moving from SNP-based to diet-based approaches, will open new directions in health – risk prediction, metabolic status assessment, assay development, biomarker design and prospective clinical studies.

8.2. Antagonistic Effects

Drug–nutrient interactions can occur through a variety of mechanisms, including changes in drug metabolism or disposition, effects on the absorption of the nutrient or drug, and alteration of nutrient endogenous synthesis, transport, utilization, or excretion. It is through this last mechanism that many dietary supplement formulations may be able to ameliorate the side effects of drug therapy 1.

Increased requirements: For many medications, chronic use may increase the body's requirement for a micronutrient due to an increase in gut excretion, a need for increased metabolic work, or an altered understanding of an essential nutrient's role. The best-known drug that alters nutritional needs in this regard is alcohol. Increased alcohol-related concerns include lower intake of important vitamins and minerals, as well as an altered understanding of their protective roles against diseases such as cancer 29. Chronic alcohol consumption has been shown to alter choline metabolism as well as the methylation of pernicious compounds.

Increased micronutrient excretion: Some medications have been shown to bind minerals in the gut or urine and hasten their excretion. Examples of medications capable of increased excretion include some diuretics, proton pump inhibitors, and chronic steroid therapy. In each case, chronic therapy increases the excretion and reduces the body's supply of important micronutrients in somewhat quantifiable amounts. These nutrient depletions have been correlated with several acute and chronic side effects, including nausea, vomiting, kidney stones, and bone health. Additionally, thiazides and some beta-blockers may enhance potassium depletion associated with 'loop' diuretics.

9. EMERGING RESEARCH ON MICRONUTRIENTS

A promising approach involves the use of food bioactives, biologically active compounds in food, to safely and effectively optimize health parameters and reduce risk for the onset and progression of chronic disease and aging. Food bioactives with proven preclinical health-promoting efficacy and human safety are consumed daily, at recommended servings within foods or as supplements. Bioactive concentrations and corresponding fortifications used big sample sizes and whole food formulations directed at populations that are largely similar with respect to ancestry, preclinic and active food bioactive screening, methods for measuring applying food bioactives, clinical and postharvest processing, and statistical approaches. In targeting population recommendations, little consideration is given to individual variation in consuming food

bioactives due to different non-homogeneous food sources, ethics, lifestyles, culture, and taste preferences. Individual variability in, for example, nutrient absorption, metabolism, and activity also are disregarded in most approaches for establishing target intake recommendations. Nevertheless, the effects of food bioactives depend on the actionable entities present, which are impacted by the integrated sequence of preclinical, postharvest, food processing, and meal preparation. Target recommendations for food bioactives need to include consideration of population parameters (quantities, duration) as well as individual-based parameters including ancestry and consumption characteristics 23. Short-term population study designs and computational approaches provide convergence of food bioactive-related data across multiple time points and references into population-centered recommendations. These approaches also facilitate targeted studies of the variation in consumption responses of food bioactives for individuals on a broader biomarker and phenome basis to prospectively develop recommendations for individuals. The importance of these approaches is illustrated in a macronutrient intake personalized study with a 2-year follow-up. Reasonable agreement was observed in the clinical, nutritional and dietary assessments procured at the earlier and later follow-up. Models of different dietary macro-, micronutrient intake, and food and drink consumption patterns were generated using the up-to-16-h-minute action food ingestion frequencies and food/chemical co-elevation biometric sampling data from a mobile application 24.

9.1. Genetic Factors

While any person with unmodified genetic risk may benefit from dietary changes, the extent of benefit may vary across individuals. Individuals who follow a poor diet in relation to their genetic risk may derive the most benefit from dietary change, whereas those with a healthy diet may be at low risk for disease regardless of genotype. Dietary recommendations made to the general population may differ in effectiveness for those with extreme genetic exposures. Modifying assumptions such that dietary changes would not result in beneficial changes in biomarker levels among certain low-risk individuals resulted in lower population impact measures 30.

The magnitude of the population impact of nutrition policies or trials, such as a tax on sugary drinks, is a function of the implementation stringency. This encompasses the extent to which they would be enacted. For example, a sugar tax of a set percentage yield smaller population impact than taxing sugary drinks only in schools. There would be value in assessing the generalisability of the trial context, and estimation of population impact of trial observations in the general population, were this evidence available. Sensitivity analyses exploring and reporting the uncertainty and plausibility of alternative assumptions would help in understanding the robustness of the observations to the chosen approach. It is critical that genuine progress towards fair policies be taken, ideally from a whole of government perspective.

An opportunity exists for a systematic approach to research prioritisation covering the breadth of roles for nutritional epidemiology and nutrition policy. Transparency on an agreed process for prioritisation would build trust across funders and stakeholders. The proportionality of investment decisions across areas of the research system may be improved. Allocating greater resources towards measurements and exposure assessment woes to build capacity which supports workforce development needs in tandem. Mechanisms to facilitate translation of research findings into effective policy and practice could also be explored further 31.

9.2. Gut Microbiome Interactions

The gut microbiome is defined as the collection of trillions of microorganisms, predominantly bacteria, in the gastrointestinal tract. The gut microbiome harbors approximately 100 times more genes than the human genome and is influenced by a variety of factors, including genetics, early-life exposure, and diet. The gut microbiome metabolizes ingested nutrients into substrates that can be utilized by the host. In turn, the gut microbiome determines the bioavailability of nutrients and potential pharmacological agents. Recent efforts to measure the abundance and activity of the gut

microbiome have suggested that the gut microbiome interacts with the gut and systemic immune system, affecting the development of a wide variety of diseases. Microbial dysbiosis has been associated with a variety of insidious disorders, including obesity, diabetes, allergies, autoimmune diseases, and Crohn's disease. Thus, the gut microbiome has a profound effect on human health, and its modification may represent an effective therapeutic approach. 32 Interactions between the gastrointestinal barrier and gut microbiome-mediated metabolism began with the establishment of the adult gut microbiome, and are underexplored as a possible mechanism explaining the genesis of diseases later in life. The gut microbiome composition remains relatively stable within individuals throughout adult life. Microbial populations are dramatically influenced by the type of dietary habits. Diet is a major factor influencing microbial diversity, microbiome composition, and its metabolic activity. Dietary changes rapidly affect the gut microbiota, which provides further evidence that diet is a potent moderating factor in the microbiome. Studies have shown that the metabolome of intestines can rapidly change after dietary changes. Reproducible changes in human intestinal microbiota composition and metabolism occurred in response to dietary modifications. It was shown that a fiber-rich plant polysaccharide diet was associated with a shift in metabolism consistent with the increase of gut butyrate-producing bacteria, a decrease in fecal pH, and increased cecal butyrate production. A less diversely composed gut microbiome was reported in humans consuming a Western diet. Traditional vegetarian and Mediterranean diets were associated with a significantly richer gut microbiome.

10. FUTURE DIRECTIONS IN MICRONUTRIENT RESEARCH

Interventions aimed at preventing chronic diseases have traditionally followed a 'one size fits all' or standardized approach. This top–down paradigm was developed based on data from epidemiological studies, during which identified dietary risk factors were incorporated into a population RDAs to inform the public and nutritionists about healthy eating. This system has had a modest success in improving public health and preventing diet-related diseases, yet is increasingly viewed as antiquated. Its limitations are becoming better understood, spurring scientists to explore alternative, more personalized, bottom–up approaches that take account of interindividual differences in dietary responses. Furthermore, it is proposed that bioactive compounds in foods and dietary patterns be used as the basis for setting target recommendations rather than traditional macronutrients, with the use of whole food interventions that are better matched to the concept of personalization than supplementation-based interventions 23.

Understanding how food bioactives relate to health is one of the most complex problems in nutrition, the reasons being, amongst others, their number, variability in food sources, food matrix effects, inability to control exposures or dose, and use of indirect markers of bioactivity or health 24. Such health promoting and disease preventing non-nutritive components of food are often referred to a food bioactives (or bioactive compounds). The biobehavioral mass short-term multivitamin/mineral intervention study is designed as a stepping stone for developing new experimental strategies for setting target recommendations. A pilot study is conducted with healthy 9–13 year olds before, during, and after a 6-week multivitamin/mineral intervention that includes compliance monitoring, genotyping, nutritional and social questionnaires, food intake and circulating plasma and urine vitamin form measurements. Most vitamin forms respond positively to the intervention and many health and clinical parameters change in expected positive directions. These observational results are interpreted using novel computational methods and therapeutic targets for optimizing vitamin intakes and interactions with health parameters are generated.

10.1. Innovative Assessment Techniques

The World Health Organization (WHO) declared 2002–2012 the "Decade of Healthy Ageing." Elimination of age-related malnutrition was included as a key strategy to promote healthy aging. The majority of the geriatric population do not get an adequate intake of

micronutrients. Malnutrition can be avoided. Diets should be improved and vulnerable populations should get food supplements or nutrient supplementation on a continuous basis. Malnutrition comes from various risk factors, including but not limited to physical, social, and medical factors. Nutrition and diet are social science issues and need to be addressed with socio-economic issues to achieve nutrient adequacy and support healthy aging. Improvement of nutrition is essential and needs a long-term focus. Addressing the nutrient status of the population means maximizing healthy life years. For such an aim, a comprehensive national action plan is needed. It consists of capacity building, development of a comprehensive prevention program including legislation, monitoring, and a benchmark of success 33. To act for improvement, the current micronutrient status of the population should be known. This act involves the assessment of precedent risk factors of malnutrition. In adolescence, it occurs mainly via the assessment of food intake. Food intake surveys are widely used to assess the nutritional status of populations. Most of the time, the conclusion is that people do not get a balanced diet because of the applied assessment tool. It might not be a valid conclusion 3. Nutritional status of the population fills a gap between food intake and health status assessments. It may be measured by valid biomarkers in biological samples. Biomarkers of dietary intake may be nutrients or metabolites in foods or metabolic intermediates. Some micronutrients may be selected with valuable representative data available for different risk groups, e.g. age and sex, some biomarkers fully fulfilling the criteria for better assessment.

10.2. Personalized Nutrition Approaches

As each individual person differs from the next in multiple ways, it is a beguiling idea that our individual nutritional needs also differ. Findings from nutritional intervention studies provide ample evidence of considerable interindividual variation in response to the same dietary exposure. It is therefore highly desirable for interventions, whether for research or for public health purposes, to be tailored to the individual, so that more effective actions can be taken 34. This review will argue that such approaches can be developed scientifically using current and emerging big data, and that they should be made available through evidence-based, ethical and user-friendly platforms. Five sections will be covered: dietary intake; interactions between diets, nutrients, genes and the gut microbiome; methods for research into individual variations; applications of personalised nutrition; and some challenges for the future.

"Nutrigenomics" is the blanket term that incorporates all interactions between diets, nutrients and their metabolites on the one hand, and the genome and epigenome on the other hand, ranging from the mechanism by which a single compound such as caffeine affects gene expression to genome-wide analyses of those dietary factors affecting the risk of a multifactorial disease 35. The area is extremely broad – with a focus ranging from molecular to population level, and applications including both basic science and public health – and thus there is considerable overlap with other contemporary topics in nutrition, such as the microbiome or the exposome. Nevertheless, from all these areas, there have emerged science-based approaches to developing dietary guidance, with the aim of making these available to "normal" people. Such guidance can take various forms, including bespoke shopping lists with specific product recommendations, or higher-level guidance on how to develop healthy dietary habits from groups of foods or meals.

11. CONCLUSION

Micronutrients, essential in the enzyme and metabolic cascades of innumerable processes within the body, are involved in processes ranging from safeguarding DNA structure to combating free radicals deriving from oxygen metabolism. All must be obtained from diet as they are not widely synthesized de novo. A myriad of health problems and diseases associated with micronutrient deficiencies are recorded daily, and it seems impossible that they are not widespread. Chronic micronutrient deficiencies impact population health and well-being and are significant public health issues worldwide, particularly in poorly developed countries. Women and children of impoverished populations are

the most adversely affected, often suffering from iron and/or folate deficiency for years on end. Pregnant women deficient in certain micronutrients may give birth to fetuses with abnormal development and low birth weight. While micronutrient deficiency is an important health issue in developed countries, it is pertinent to note that supplementation is not always a benefit and that excessive intake might also elicit side effects.

So far, this review has had a focus not on why and how nutrient insufficiencies should be addressed. Rather, it documents their truly staggering extent, speed of increase, and the requirement for sophisticated widespread diagnostics to inform this. Furthermore, the need for efficacious public health initiatives to ameliorate micronutrient deficiency in population health is noted. Combined with this need is the paradox that such initiatives are remarkably, and at times shockingly, poorly used in the general populace. An example, Diet DISH, was designed to be delivered in a classroom setting with teachers taking the lead with students and parents. It was designed to be a broad based approach where all participants would engage in making a specific menu for all meals throughout the day using locally available ingredients to minimize cost. Materials were developed as broadly as possible and delivered to teachers as a uniform package to minimize the chance of any bias in the results 23. However, usage rates ranged from 811% with stating "...these instructor-led interventions are less effective than expected." Amongst the interventions, Vegemite, and preference purchase were a significant success driven at any time of the day. It would be hoped that food must taste good to persuade people to purchase it. Similarly, Nutri-butter was used in 11% of the time intervals and is a significant consideration where low taste is a barrier to purchase. A surprising outcome was that twister and YoPro were not increased at all post intervention despite being highly effective.

Thus, it is expected with the phytoacchemical test, down the line would contribute to better engaging and treating patient populations and clinicians alike upon conducting trials.

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