ISSN-Online: 2320-787
ISSN-Print: 2319-1775

REVIEW ARTICLE

Health Impacts of Micronutrient Deficiencies on Humans—A Review

Manju I[1], Mohamed Malik S[2], Srinivasan K.S[3], Naveen Kumar S[4], Vairaperumal K[5], Malini Prithiva Kumari P K[6]

[1,3]ECE, Professor, Mohamed Sathak A J College of Engineering, [2,4]ECE, Asst. Professor, Mohamed Sathak A J College of Engineering, [5]EEE, Asst. Professor, Mohamed Sathak A J College of Engineering, [6]Student, Sri Ramachandra Institute of Higher Education and Research

ABSTRACT Micronutrient deficiencies continue to be one of the major etiological factors and an inevitable part in epidemiology in combating disease. Vitamins and minerals (Micronutrients) are essential for healthy development of human body and disease prevention. The current study and review were done to update information on micronutrient deficiencies, understand their influence on the healthy/unhealthy people in various age groups. Understanding the minimum requirements of micronutrients for human wellbeing, its correlation in alleviating diseases, identifying those at risk are vital in identifying treatment to reduce the comprehensive burden of disease, especially in low- and middle-income countries. Awareness campaigns on causes and risk of malnutrition, balanced diet, supplementation and fortification of essential nutrients and other health care approaches for the high-risk population are the need of the hour in the global pandemic.

Keywords: Micronutrient deficiency, Malnutrition, Vitamins and minerals, Anemia, Vitamin B, Vitamin D, Vitamin A

Address for correspondence: Manju I, Professor, Mohamed Sathak A J College of Engineering, Chennai, Tamil Nadu 603103, India. E-mail: manjujackin@gmail.com

Submited: 17-Jan-2021 **Accepted:** 22-Jun-2021 **Published:** 26-Jul-2021

INTRODUCTION

According to the World Health Organization, Malnutrition refers to insufficiencies, overindulgences, or imbalances in a person's consumption of food/nutrients. Malnutrition is caused by under nutrition, micronutrient shortages, obesity, overweight and diet-related non-communicable diseases [1]. Vitamins and minerals or Micronutrients, are mandatory to healthy physical and mental development, disease inhibition, wellbeing and cannot be produced by the body [2]. Globally, at least 50% of the children in the 0-5 year's age group are affected by vitamin and mineral deficiencies [3].

Vitamins like Vitamin A, B12, D and minerals such as iron, manganese, zinc, fluoride, calcium, selenium, copper, chromium, iodine, molybdenum, aluminum, cadmium, mercury, arsenic, lead are required in tiny quantities. These micronutrients empower the human body to produce different compounds and hormones required for proper functioning and deficiency can cause dangerous health conditions [4].

Access this article online
Website: www.ijfans.org
DOI: 10.4103/ijfans_13_21

Anemia is a predominant nutritional/dietary problem that is significantly prevalent in throughout the world, especially in developing countries. Anemia ensues due to the lack of haemoglobin (Hb), a protein contained in red blood cells that is responsible for delivery of oxygen to the tissues [5]. The incidence of Anemia in Southeast Asia is one of the highest in the world, with more than 616 million people at risk [6]. According to a study done in 2014 on the trends of underweight and obesity, South Asia ranks first in underweight category [7]. UNICEF, WHO and World bank report estimates 87 million children suffered from stunting, 20 million are overweight and 36 million were severely malnutrition in Asia in 2017 [8]. In developing nations, nearly 45% of deaths among children belonging to 0-5 years of age is attributed to under nutrition [9] [8], [10]. In India, 30-40% of children are stunted, more than 15% are severely malnutrition and less than 5% are overweight [2]. In typical

How to cite this article: Manju I., Mohamed Malik S., Srinivasan K.S., Naveen Kumar S., Vairaperumal K, Malini Prithiva Kumari P. K. Health Impacts of Micronutrient Deficiencies on Humans—A Review. Int J Food Nutr Sci 2021; 10(3):1-12.

Table 1: Classified Anemia Deficiency in Different Age Population

Age Population	Non-Anemia*	Anemia*		
		Mild[a]	Moderate	Severe
Children 6 - 59 months of age	110 or higher	100-109	70-99	lower than 70
Children 5 - 11 years of age	115 or higher	110-114	80-109	lower than 80
Children 12 - 14 years of age	120 or higher	110-119	80-109	lower than 80
Non-pregnant women (15 years of age and above)	120 or higher	110-119	80-109	lower than 80
Pregnant women	110 or higher	100-109	70-99	lower than 70
Men (15 years of age and above)	130 or higher	110-129	80-109	lower than 80

individuals, hemoglobin levels and requirements vary with the gender, development phase, hormonal stimulus, and oxygen levels. The cut-off hemoglobin limit is established by the World Health Organization (WHO) to define iron deficiency Anemia are shown in Table 1 [11].

Vitamins comprise of four lipid-soluble vitamins (vitamins A, D, E, and K) and nine water-soluble vitamins (vitamins B1, B2, B6, B12, niacin, pantothenic acid, folic acid, biotin, and vitamin C). Lipid-soluble vitamin deficiency is caused by decreases in intake of lipid-soluble vitamins and lipid absorption. Hypervitaminosis occurs lipid-soluble vitamins are consumed in excess and get accumulated in the liver and fat [9]. Vitamin and mineral deficiencies in adults result in increased probability of Anemia/infections, decrease in intellectual reasoning and poor wound healing [12]. World Health Organization (WHO) explained adolescence both in term of age (spanning the age between 10-19 years) and in terms of phase of life marked by special attributes shown in Table 1. Adolescent girls are at high risk of micronutrient malnutrition especially iron deficiency anemia. Globally the primary cause of anemia in adolescent girls is iron deficiency due to improper dietary intake, rapid physical growth at puberty and iron losses during menstruation cycle. Other prevalent causes of anemia include, malaria, chronic infection, and dearth of vitamin A, vitamin B12, folate and vitamin C is a well-known enhancer of iron bioavailability [13].

Classification of public health significance of anemia in populations based on prevalence estimated from blood levels of haemoglobin established in Table 2.

Table 2: Classification of Public Health Significance of Prevalence of Anemia

Category of Public Health Significance	Prevalence of Anemia (%)
Severe	40 or higher
Moderate	20.0 – 39.9
Mild	5.0 – 19.9
Normal	4.9 or lower

MATERIALS AND METHODS

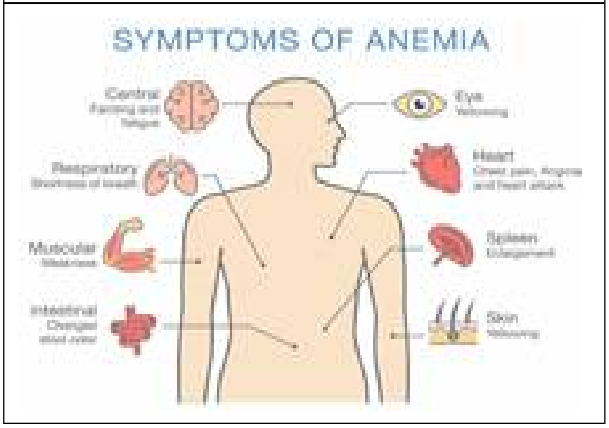
A review was done on literature extracted from PubMed, Google Scholar, and Web of Science databases published within the time 1960-2021. Original articles as well as review articles that included organized reviews and meta-analyses were studied. Articles in English language were alone considered. The chosen elements were Iron, Vitamin B12, Vitamin D, Vitamin A and other minerals. The deficiencies studied included Anemia, Vitamin B deficiencies, Vitamin D deficiencies, Vitamin A deficiencies and other mineral deficiencies. The search strategy included the following keywords: anemia, malnutrition, micronutrient deficiency, Vitamin B deficiency, Vitamin D deficiency, Vitamin A deficiency. Around 110 articles were assessed as relevant to the topic and included in the review.

Anemia

Anemia is caused by inadequate amount of red blood cells which results in insufficient oxygen supply to the body's tissues. The types of anemia are Iron deficiency anemia, Vitamin deficiency anemia, Sickle cell anemia, Aplastic anemia, Thalassemia [14]. Iron deficiency anemia manifests when the production of erythrocytes is not sufficient due to decreased iron [8] [15] intake and iron stores are insufficient or when there is a rapid loss of iron. This disease does not cause death, but causes a significant impact on health like sever fatigue, pregnancy complications, heart problems and rarely death [5] [16] [17] [7-10, 17]. The Prevention and successful treatment for iron deficiency anemia is still a challenge because it is frequently disregarded by doctors in developed/ industrialized nations [18] and malnutrition in third world countries. The major causes of iron deficiency anemia during prenatal and postnatal stages are malnourishment or merger

iron in the diet, blood loss, a decreased ability to absorb iron [19]. Figure 1 shows symptoms of anemia in health consequences of anemia on infant, children, pregnant women, and elderly are discussed below [20].

Figure 1: Symptoms of Anemia in Human



Anemia in Children

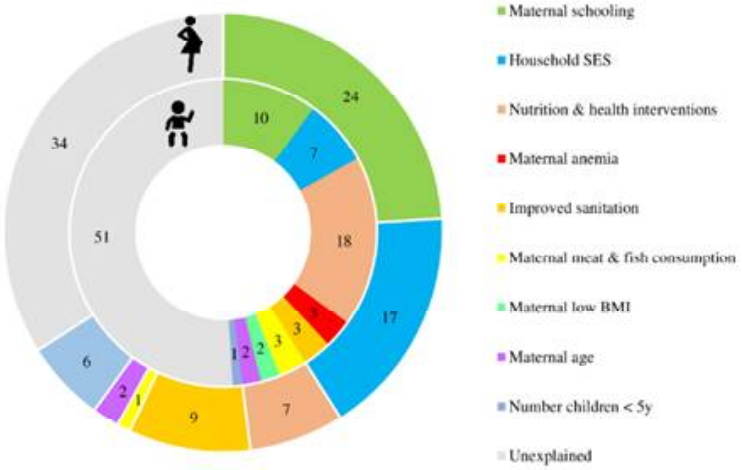
In children, major health consequences include stunting, reduced cognitive development, thinned/wasted physical growth, increased mortality and frequent sickness [21] [22]. Birth weight, sex of household head, age of household head, maternal education, wealth status, size of household, source of potable water and country of residence are some of the factors affecting anemia in children according to a survey done among children under the age of 5 in Sub Saharan Africa [23]. Adolescence is the period of development in which profound amount of change in human development namely biological, cognitive, psychosocial, and emotional domains [24] [25] [26]. Adolescence is characterized by physiological changes such as change in height, weight, sex characteristics, circulatory and respiratory systems that are influenced by hormonal activity [24]. However the change in one domain will influence and result in significant, cascading and potentially long-term effects in functioning in other domains [25]. For example, brain development in the limbic system related to pleasure seeking, reward processing, emotional responses, sleep regulation, etc., occur during this period and simultaneously changes in pre-frontal cortex that affect an individual's decision-making capacity, handling of impulse and planning for the future also happen [26].

To treat anemia in infants and adolescent children, emphasis must be given to the awareness and intake on natural and supplementary foods that contain of iron, folic acid, vitamin B-12, calcium, zinc, and protein. School based nutrition education has potential to improve dietary practices that affect young person's health, growth, and intellectual development [27].

Anemia in Pregnant Patients

Anemia during pregnancy is caused by multiple factors and is influenced by geographical location of the subject, socio-economic conditions, trimester, and dietary practice. During pregnancy, in order to maintain/sustain adequate placental and fetal growth and accommodate blood loss during delivery iron requirements increase approximately 10-fold from 0.8 mg/day in the first trimester to 7.5 mg/day in the third trimester [28] [29] [30]. Maternal anemia affects 32 million women worldwide [31] [32]. A study based on UK cohort reported an occurrence of anemia in 46% of women at some point during pregnancy [33]. In developing countries, anemia during pregnancy is due to micronutrient deficiencies and parasitic diseases [34]. It causes increased maternal, perinatal morbidity and mortality and neurocognitive deficits in infants. Twelve percentage of low birth weight, nineteenth percentage of preterm births and eighteen percentage of perinatal mortality is attributed to Maternal anemia [35]. Figure 2 describe analysis in

Figure 2: Analysis in Haemoglobin Factors Pregnant Women and Children



hemoglobin factors affected among pregnant women and children from Indian strategical report from 2006 to 2016 [36].

Anemia in Elderly Patients

Prevalence of Anemia in elderly patients increases with age [37] [38] [39]. In the elderly, the reasons that lead to Anemia are chronic diseases (30-45%), Iron Deficiency (15-30%), after haemorrhage (5-10%), cancer (5%), Vitamin B12 and folate deficiency (5-10%), and unexplained causes (15-25%) [40] [41].

The common nutrient deficiencies that are prevalent among the elderly are due to calcium, iron and folic acid deficiency [40]. In order to provide necessary treatment it is imperative to identify, measure these deficiencies [41]. Anemia in elderly can augment other diseases and result in severe complications, including impaired physical functioning [42], decreased functionality [43], multidimensional loss of function [44], increased risk of frailty [45] [46] [49], depression [50], cognitive impairment [51], obstructive sleeping apnea [52], frequent comorbidity and hospitalization [53] [54] [55], and increased risk of death [54] [56] [57]. In summary, Anemia severely affects quality of life, social status, economic status, health and vulnerability in older persons [58].

Probability of occurrence of anemia is high in cirrhotic patients. The probable causes are hepatitis and chronic alcoholism, iron/vitamin B12/folate deficiencies, alcohol-induced marrow aplasia or anemia because of viral liver disease [59] [60]. Table 3 describe causes and distribution for anemia in elderly patients [61].

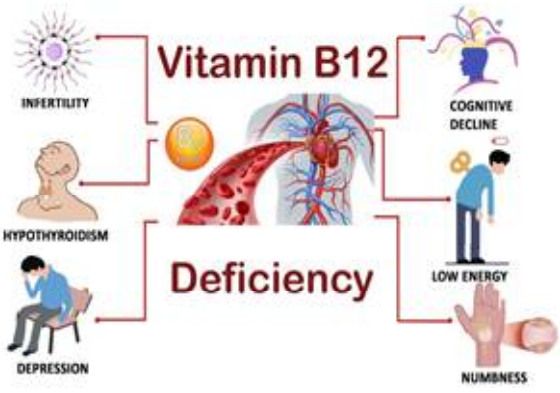
Table 3: Causes and Distribution for Anemia in Elderly Patients

Cause	Distribution
Iron-deficient erythropoiesis Anemia of chronic disease Iron deficiency	30-45%
Vitamin B12 or folate deficiency	5-15%
Renal disease	5-15%
Myelodysplasia	5%
Other	15-35%

Vitamin B12 Deficiencies

Vitamin B12 is a water-soluble vitamin, required for healthy red blood cell development, neurological function, and DNA synthesis [59-63]. It is naturally found in animal products such as fish, poultry, meat, eggs, milk, and dairy products and is generally not present in plant food [62]. Therefore, vegetarians are of high risk of having vitamin B12 deficiency [63] [64] [65]. A systematic review of the prevalence of vitamin B12 deficiency among vegetarians using serum levels found that it was noted in up to 11-86.5% in different age groups of vegan patients [65]. Gluten-free food lack minerals (calcium, iron, magnesium, and zinc), vitamins (vitamin B12, folate, and vitamin D), and fibers [66]. In fact, for Celiac Disease patients who are forced to take life-term gluten-free diet, a micronutrient deficiency was detected in up to 30% of subjects for vitamin B12, 40% for iron and zinc, and 20% for folic acid and in children for magnesium, and 25% for vitamin D [67]. This emphasizes the need for continuous monitoring and dietary supplementation of these micronutrients. Figure 3 shows the identical deficiency in Vitamin B12 [68].

Figure 3: Identical Deficiency for Vitamin B12



Furthermore, Vitamins B9, B12, B6 that are essential for homocysteine metabolism, physiological and neurological working in young children [69]. Vitamin B12 and folate (also known as folic acid or vitamin B9) dependent enzyme methionine synthase play an important role in brain development [70]. However these nutrients that cannot be produced in the body and must be supplied by the diet [71] [72] [73]. The decreased Vitamin B12 levels increased the antioxidant requirement leading to neuropsychiatric problems due to free radical formation in Aging, Autism and Schizophrenia patients [74].

Infantile Tremor Syndrome (ITS) is a nutritional deficiency syndrome characterized by tremors, muscle weakness, anemia, pigmentary disorders and retarded mental development [75]. It is caused by vitamin B12 deficiency [76]. Treatment with vitamin B12 resulted in dramatic improvement of health in 27 infants aged 6 to 27 months of vegetarian mothers with symptoms of developmental delay, paleness, hyper-pigmented skin, and sparse brown hair [77].

Vitamin D Deficiencies

Vitamin D is produced as vitamin D3 in the skin under the stimulus of sunlight/ultraviolet radiation or by the intake

through the diet/supplements. The natural production of vitamin D3 is influenced by exposure to sunshine, latitude, types of clothes, and the use of sun block/pigmentation creams [78]. Though Vitamin D is generally lower in countries lying in higher latitudes and with darker skin types, it is also prevalent in countries lying lower latitudes and in countries which have implemented vitamin D fortification schemes [73]. Figure 4 shows survey benchmark on concentration in blood for female in vitamin D Deficiencies [79].

Vitamin D deficiency can cause softening and weakening of bones (rickets) in children and antagonistic effects on skeletal health in all age groups. It precipitates and aggravates bone disorders like osteopenia, i.e., decrease in bone mass, brittle bones or osteoporosis, and fractures in adults [80]. Vitamin D deficiency has been associated with increased risk of skin cancers, autoimmune diseases like arthritis/multiple sclerosis, diabetes, hypertension, metabolic syndrome and infectious diseases [81] [80] [82] [83].

The differential effects of vitamin D on sarcopenia between male and female participants have been reported to be caused by biological factors such as anabolic hormones (e.g., androgens, growth hormones), cytokines involved in muscle catabolism (e.g., glucocorticoids), and even genetic polymorphisms (e.g., vitamin D receptor), hypothesised that vitamin D Binding Protein (DBP), which is a transporter of vitamin D to target tissues, may play a role in gender differences in vitamin D status [84] [85]. Vitamin D stores impact the mental and psychomotor functions of children [86].

Below Table 4 shows Selected Vitamin Deficiencies are listed:

Figure 4: Benchmark Report for Vitamin D Deficiencies

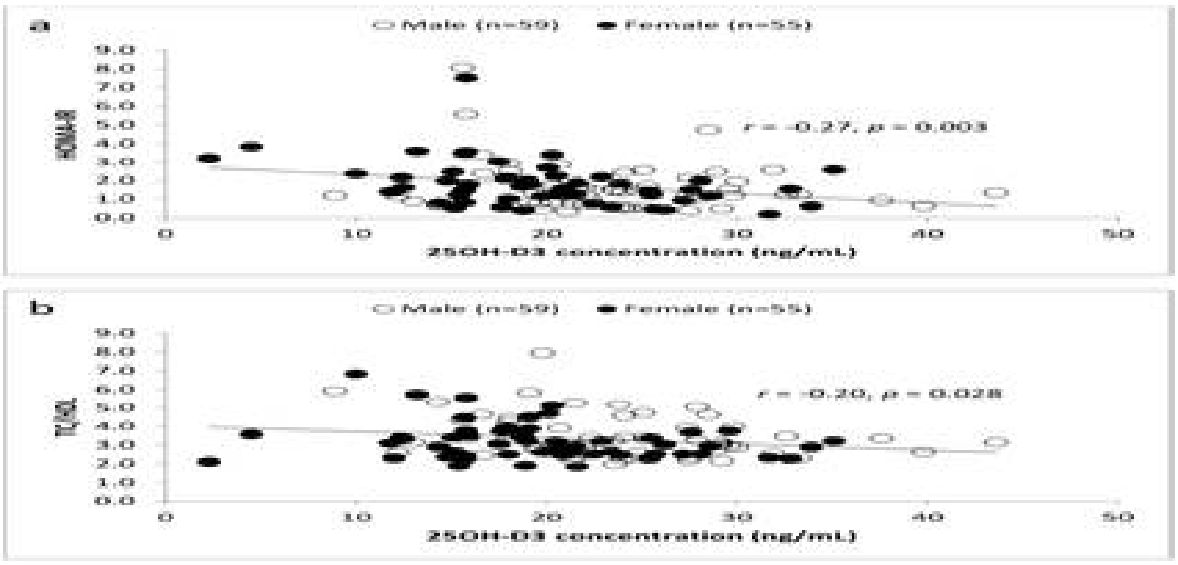


Table 4: Selected Vitamin Deficiencies

Vitamin	Signs and Symptoms of Deficiency	Cause	Laboratory Assay	Treatment
Vitamin B12	Pernicious Anemia, glossitis, spinal cord degeneration, Spinal cord degeneration, Weakness, loss of balance.	Decreased absorption in the elderly, loss of gastric intrinsic factor, malabsorption disorder.	Serum B12	Vitamin B12 injection, oral B12
Vitamin C	Impaired wound healing, bleeding, ecchymosis, swollen gums, anemia, enlargement and keratosis of hair follicles.	Inadequate consumption in diet, smoking, hemodialysis.	Plasma ascorbic acid	Consuming foods rich in vitamin C;
Vitamin D	Rickets in children, osteomalacia in adults, muscle weakness, increased risk of fractures	Lack of sun exposure, hepatic or renal disorder, anticonvulsant drug therapy	Plasma 25-hydroxy vitamin D	Consuming milk and other beverages fortified with vitamin D

Vitamin A Deficiency

Vitamin A comprises of a group of fat soluble retinoid, including retinol, retinal, and retinyl esters [87] [88] [89]. Vitamin A affects the immune system, vision of the person, the reproductory system, and communication between cells [90] [91]. Globally vitamin A deficiency (VAD), affects around 190 million children under five years of age. In humans, VAD increases the risk of night blindness, bitot's spots, and mortality due to infectious disease such as measles, diarrhea and respiratory disease among children [92] [93] [94].

According to WHO, VAD is prevalent across the globe and was affecting more than 30% of children aged 6months-5yrs, 50% of whom are in Southeast Asia and about 44% in Africa. The report further states that more than 90 million preschool children are affected with subclinical VAD around the world [93]. In India, the prevalence of subclinical VAD was 37% among preschool children and 25% among NPNL women and 32% among pregnant and lactating women [95]. Figure 5 shows comparison for body weight, fat weight, liver vitamin A, Vitamin A signaling, serum Vitamin A [96].

Post-operative pregnancies, such as pregnancies after bariatric surgery also increase the possibility of birth defects due to imperfect absorption of food after surgery, congenital anomalies caused by vitamin A deficiency. In a sample group of six patients, a clinical pattern was characterized by delay in psychomotor development (100%), microphthalmia (83%), retardation in growth (66%), varying degrees of deafness (66%), and variable facial dysmorphism [97]. Figure 6 shows flow diagram for Vitamin A deficiency in various concerns [98].

Figure 5: Comparison Chart for Various Problem on Vitamin A Deficiency

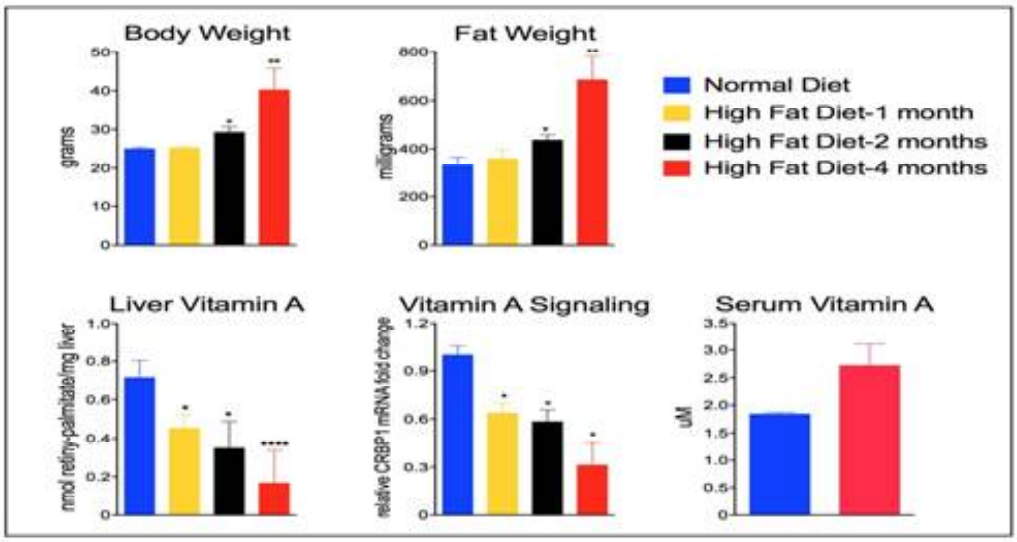
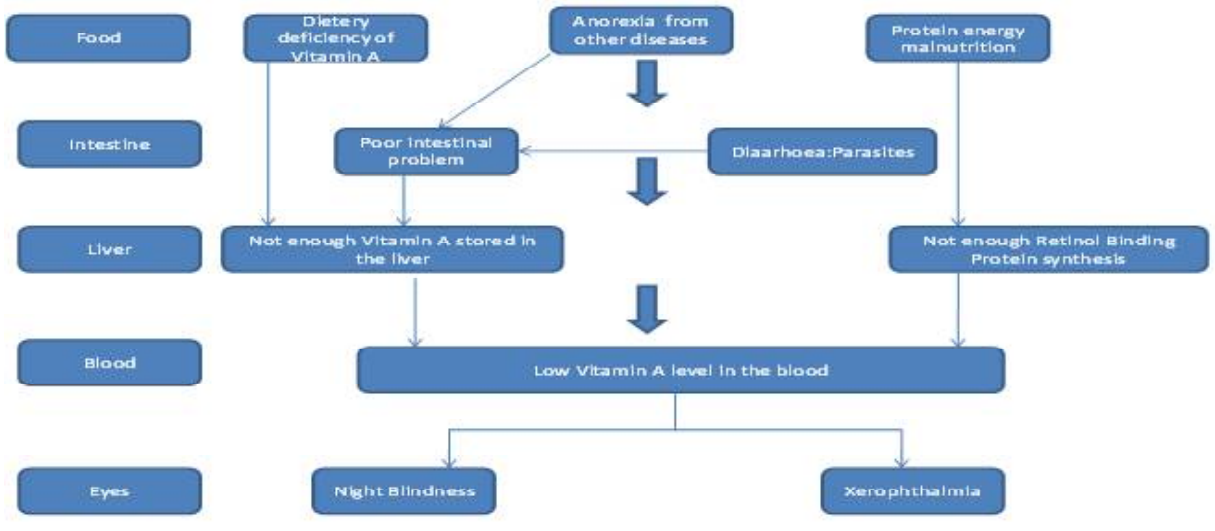


Figure 6: Flow Chart Based on Various Aspects in Vitamin A Deficiency



Other Mineral Deficiencies

Minerals such as iron, calcium, zinc, iodine, sodium, copper, chromium, manganese, potassium, molybdenum, aluminum, cadmium, lead which are present in living tissues are called Trace elements/metals. Their primary functions are regulation of immunity, nerve conduction, enzymatic reactions, muscle seizures, regulation of membrane potential and mitochondrial activity. Variations in the trace elements like magnesium, potassium, sodium result in Hypermagnesemia, hypomagnesaemia, hyperkalemia, hypokalemia, Hypernatremia and hyponatremia [99]. These abnormalities can cause cardiac arrhythmia and can result in cardiac arrest.

The decrease in phosphate, magnesium, potassium, sodium and calcium, and other elements in blood plasma are attributed to chronic alcohol consumption [100] [101] [102]. Hypokalemia, hypomagnesaemia, and hyponatremia are observed in patients in alcohol withdrawal Alcohol withdrawal and hypokalemia: A case report. [103] [104] [105] [106] [107] [108]. Hence proper monitoring of these minerals are required to recommend either oral or intravenous supplementation of relevant electrolytes in order to maintain their appropriate physiological ranges.

Micronutrients like Vitamin A, C, D, E, Iron, Zinc and Selenium are reported to act against respiratory Infections. These are immune Nutrients which is said to have anti-viral properties. Consumption of these immune nutrients helps to protect from any respiratory infections [109].

CONCLUSION

Vitamins are required for growth and proper functioning of the body. While minerals, contribute to the energy metabolism and maintenance of the body. These micronutrients are essential for normal functioning and disease-free life.

According to a report published by the World Health Organization (WHO), 43% of children aged 6 months-5 years, 38% of pregnant women and 29% of non-pregnant women were anemic in 2011. Southeast Asian countries contribute a major share of the above numbers with 54% children, 49% pregnant women and 42% non-pregnant women affected by anemia. Of these, 59% of children, 54% of pregnant women and 48% of non-pregnant women were from India [110]. Inspite of the many government initiatives taken by the Government of India to eradicate malnutrition in India, factors like socio-economic status, domestic violence, population, dual burden of malnutrition etc., much remains to be done.

Normally testing for micronutrients is done at the request of the physician for diagnostic reasons or as part of a routine blood test done annually. The psychological mind set of the Indian population and the availability of testing facilities and resources is varied and depends on the persons socio-economic status, gender, age, region, etc. Most of the patients seek medical intervention only in advanced stages of disease compounded by malnutrition.

Hence early detection of micronutrients, using technologies like IoT, artificial intelligence, mobile apps, cloud computing will help diagnosis, use of appropriate strategies for dietary improvement and food fortification. A handheld device that tests micronutrient deficiency will help in keeping our children and elderly safe.

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