ZITA MEDICAL MANAGEMENT

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ΦΑΡΜΑΚΕΥΤΙΚΗ, 35, ΙΙΙ, 2023 | 28-37 ΑΡΘΡΟ ΕΠΙΣΚΟΠΗΣΗΣ

PHARMAKEFTIKI, 35, III, 2023 | 28-37 REVIEW ARTICLE

Role of Vitamins and Minerals in Treating Certain Health Conditions: A Review of Current Opinion

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KEYWORDS:
Vitamins; minerals; cardio-vascular diseases; diabetes; cancer; immune system; osteoporosis; COVID-19; HIV.

ARTICLE INFO:
Received: November 10, 2022
Revised: February, 2, 2023
Accepted: March 24, 2023
Available on line: September 4, 2023:

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ABSTRACT

The role of vitamins and minerals is considered of paramount importance in management of human health. The per day dietary requirement of vitamins and minerals have been standardized. The deficiency diseases have also been spelt out. The excess of some of these supplements is also documented to cause health problems. The correct quantity required for human being has always been subject of discussion. The aim of this review article is to present an overview of the latest opinion of experts in the subject area. The review articles and research papers on effects of vitamins and minerals on certain diseases, e.g., cardiovascular disease, cancer, diabetes, weak immune system response, HIV/AIDS, COVID-19, and osteoporosis, were consulted. The present article gives a brief idea about vitamins and mineral, their daily requirement, deficiency diseases and critically examines the current views on effect of vitamins and minerals on health conditions mentioned.

1. Introduction

1.1 Vitamins and minerals

Vitamins and minerals are among highly taken supplements by the human being across the globe.[1,2] The term vitamin ("vita" meaning life and "amine" signifying nitrogenous substances essential for life) was first coined in 1912 by the biochemist Casimir Funk, who is known as father of vitamin therapy.[3,4] Vitamins are organic compounds required in very small quantities for certain body functions that the body cannot synthesize. An exception is Vitamin C which is required in fairly high quantity. Thus, vitamins must be supplied with

diet. The deficiency of vitamins is well known to lead to certain diseases. All vitamins were discovered from 1912 to 1948. The commercial production of vitamins started in 1948.

Minerals occur in soil and water and are absorbed by plants or eaten by animals. Minerals too are extremely important for human health. Human beings get most of the minerals from the diet consisting of plant and animal products or from drinking water.[5] While many of us are familiar with sodium, calcium, potassium, there are other minerals such as trace minerals like zinc, copper, and iodine that are required by body in small amounts. Minerals are important in growth of stronger bones and teeth, controlling the body fluids inside and outside cell, and releasing energy from the food. For example, bone health and hemoglobin level are managed by administration of calcium and iron minerals, respectively. Iodine deficiency is known to cause goiter disease that causes enlargement of thyroid gland. During COVID-19 management vitamin C and mineral zinc were commonly prescribed vitamin and mineral.

1.2 A simple classification of vitamins

Earlier nutritional studies have classified vitamins into two groups – water-soluble vitamins and fat-soluble vitamins. Water-soluble vitamins included vitamin B_1 (thiamine), vitamin B_2 (riboflavin), Vitamin B_3 (Niacin), vitamin B_6 (pyridoxin), vitamin B_{12}, vitamin H (biotin), folate and pantothenic acid (vitamin B_5). The fat-soluble vitamins are vitamin A (b-carotene), vitamin D (calciferol), vitamin E (α-tocopherol) and vitamin K. All water-soluble vitamins except vitamin C and the only fat-soluble vitamin, vitamin K are precursors of coenzymes. The body synthesizes coenzymes from them. Coenzymes are organic molecules that assist enzymes in catalyzing certain reactions that cannot be catalyzed alone by the amino acid side chains of the enzyme.[6] A list of some common coenzymes synthesized from vitamins and the deficiency diseases are listed in Table 1.

1.3 Dietary reference intakes (DRI) for vitamins and minerals

The National Academy of Medicine, USA, has developed nutrients reference values called dietary reference intake (DRI) based on deficiency and toxicity of nutrients reported. The DRIs are specific to age, gender, and life stages, and cover over 40 nutrients. The DRIs for common vitamins and minerals are presented in Table 2.

1.4 Occurrence, availability and uses

Water-soluble vitamins occur mainly in grains, fruits, vegetables, milk and dairy foods. Fat-soluble vitamins are found mainly dairy foods, vegetable oils, animal fats, liver, and oily fish.[8] Minerals occur in fruits, vegetables, milk, dairy foods, meat, fish, cereals and nuts.[8] Vitamins and minerals, as industrial manufactured

Table 1. Vitamins, coenzymes synthesized and deficiency disease in human being.

Vitamin	Coenzyme	Deficiency diseases in human
Vitamin B_3	NAD^+, NADH	Pellagra
Vitamin B_2	FAD, $FADH_2$	Skin inflammation
Vitamin B_1	TPP	Beriberi
Pantothenic acid	CoASH	Paresthesia
Vitamin H	Biotin	Dermatitis
Vitamin B_6	PLP	Anemia
Vitamin B_{12}	Coenzyme B_{12}	Pernicious anemia
Folic acid	THF	Megaloblastic anemia
Vitamin K	Vitamin KH_2	Internal bleeding

supplements can be easily purchased over the counter in pharmacies. There are some reports suggesting that more people in developed countries like USA and UK take vitamins and supplements in comparison to people of middle-income and low-income countries.[9] Also, the consumption is usually higher in relatively more educated people. Other people take them only when some deficiency disease is diagnosed, and doctor prescribes them. However, the role of vitamins and mineral supplements in healthy people has always been subject

Table 2. Recommended Daily Requirement of Vitamins and Minerals for Human Being.

Vitamins (Common Names)	**Recommended Dietary Allowance (RDA) or Daily Adequate Intake (DAI)***		**Upper Limit**
	Women	**Men**	
Thiamine	1.1 mg	1.2 mg	Not known
Riboflavin	1.1 mg	1.3 mg	Not known
Niacin	14 mg	16 mg	35 mg
Pantothenic acid	5 mg*	5 mg*	Not known
Pyridoxin	Age 19-50: 1.3 mg Age 51+: 1.5 mg	Age 19-50: 1.3 mg Age 51+: 1.7 mg	100 mg
Biotin	30 μg*	30 μg *	Not known
Folate	400 μg	400 μg	1,000 μg
Vitamin B12	2.4 μg	2.4 μg	Not known
Ascorbic acid	75 mg * (+ 35 mg for smokers)	90 mg * (+ 35 mg for smokers)	2,000 mg
Carotene	700 μg (2,333 IU)	900 μg (3,000 IU)	3,000 μg (about 10,000 IU)
Calciferol	Age 19-50: 15 μg (600 IU) Age 51-70: 15 μg (600 IU) Age 71+: 20 μg (800 IU)	Age 19-50: 15 μg (600 IU) Age 51-70: 15 μg (600 IU) Age 71+: 20 μg (800 IU)	100 μg (4,000 IU)
Tocopherol	15 mg	15 mg	1,000 mg
Vitamin K	90 μg *	120 μg *	Not known
Minerals	**RDA and DAI***		**Upper Limit**
	Women	**Men**	
Calcium	Age 31-50: 1,000 mg Age 51+: 1,200 mg	Age 31-50: 1,000 mg Age 51+: 1,200 mg	2,500 mg
Chloride	Age 19-50: 2.3 grams* Age 51-70: 2.0 grams* Age 71+: 1.8 grams*	Age 19-50: 2.3 grams* Age 51-70: 2.0 grams* Age 71+: 1.8 grams*	Not known
Chromium	Age 31-50: 25 μg * Age 51+: 20 micrograms*	Age 31-50: 35 μg * Age 51+: 30 μg *	Not known
Copper	900 μg	900 μg	10,000 μg
Fluoride	3 mg	4 mg	10 mg

Iodine	150 μg	150 μg	1,100 μg
Iron	Age 31-50: 18 mg Age 51+: 8 mg	Age 31-50: 18 mg Age 51+: 8 mg	45 mg
Magnesium	Age 19-30: 310 mg Age 31-70+: 320 mg	Age 19-30: 400 mg Age 31-70+: 420 mg	350 mg (from supplements)
Manganese	1.8 mg*	2.3 mg*	11 mg
Molybdenum	45 μg	45 μg	2,000 μg
Phosphorus	700 mg	700 mg	Age 19-30: 310 mg Age 31-70+: 320 mg
Potassium	Age 19-30: 310 mg Age 31-70+: 320 mg	Age 19-30: 310 mg Age 31-70+: 320 mg	Not known
Selenium	55 μg	55 μg	400 μg
Sodium	1,500 mg*	1,500 mg*	Not known; however, a chronic disease risk reduction intake has been proved.
Phosphorus	8 mg	11 mg	40 mg

** Denotes Adequate Intake (DAI). An AI is a recommended intake when an RDA can't be determined. RDA is the average daily dietary intake required to provide the sufficient nutrient in 97-98% of healthy people in a particular group according to different stages of life and gender.*

of discussion.[9] Evidently, taking supplements will not allow deficiency to occur. The excess water-soluble vitamins are excreted from the body with urine. However, the fat-soluble vitamins may accumulate in the body and can be harmful, causing hypervitaminosis.[10] So, there must be check and balance on their intake. One should not forget a rule of thumb: excess of anything is bad" and this is true in case of vitamins and minerals as well. It should also be kept in mind that supplements are not substitutes of a balanced healthy diet.

2. Effect of Vitamins and Minerals on Different Health Conditions

The role of vitamins and minerals in preventing, countering or managing certain health conditions such as cardio-vascular diseases, type-2 diabetes, cancer, HIV/AIDS, COVID-19, immune system response, and osteoporosis, etc. have been studied and reported. Zhang and his colleagues have analyzed the health effects of vitamins and minerals on cardio-vascular diseases, cancer, type-2 diabetes, and osteoporosis.[9] In the following sections, a brief overview of the analysis by Zhang and coworkers,[9] and of the effects of vitamins and minerals on some other medical conditions such as HIV/AIDS, immune system response and COVID-19 is presented.

2.1 Effect on cardio-vascular diseases

The death by cardiovascular diseases is a matter of concern in the USA. It is also becoming very common among youth in India and other developing countries. Benefits of taking vitamins and mineral supplements in preventing the cardiovascular diseases in young healthy people have been studied. The US Preventive Service Task Force (USPSTF) published a review in 2013,[11] After this review, a paper on systematic review of fifteen randomized trials has been published. This review paper concluded that there was no benefit whatsoever of supplements on cardiovascular diseases, mostly among patients with risk factors.[12] Although randomized trials of folic acid, alone or in combination with vitamins B_{12} or B_6 led to significant lowering of plasma homocysteine levels, total cardiovascular episodes were not diminished. Another comprehensive

review paper based on a large trial conducted in China has mentioned a lower risk of stroke in combination with supplementation of homocysteine lowering vitamins B.[13] Also, there is no conclusive evidence to advise supplementation with antioxidants for minimizing the cardiovascular risk.[11,14] There was no effect of supplementation with vitamin D (2000 IU/ day) as well on its primary endpoint (myocardial infarction, stroke, or cardiovascular death) in healthy people.[15] A combination of calcium and vitamin D also showed no effect on cardiovascular risk in a large scale trial.[16,17]

2.2 Effect on cancer

The evidences available in literature till date do not support effect of vitamins and minerals in preventing occurrence of cancer. Indeed, there are some studies that suggest harmful effects of some supplements on certain types of cancer.[9] Some investigations have been carried out on the possible role of vitamins A, D, E and folic on selected types of cancer that are discussed below.

Two randomized trials suggested increased risk of lung cancer among high-risk person on β-carotene supplementation. A study carried out on cancer prevention using α-tocopherol and β-carotene revealed an 18% increase in relative risk among people who smoke randomized to β-carotene (20 mg/day) compared with those who were not supplemented.[18] A trial conducted on β-carotene and retinol efficacy demonstrated that a combination of β-carotene (30 mg/day) and vitamin A as retinol (25 000 IU/day) increased the risk of lung cancer by 28% among smokers and workers having occupational exposure to asbestos.[19] In 2014, the US Preventive Services Task Force (USPSTF) recommended not to use β-carotene or vitamin E for prevention of cancer as there was no enough evidence to assess the net benefit of multivitamins or the use of single- or paired-nutrient supplements.[20]

A multivitamin supplementation is reported to have some benefit for cancer incidence. In pooled analyses of 84 investigations (N = 739 803), multivitamin supplementation significantly reduced the i) cancer occurrence of any type (odds ratio, 0.93 [95% CI, 0.87-0.99]; 4 RCTs [n=48 859]; absolute risk difference (ARD), range among adequately powered trials, -0.2% to -1.2%) and, ii) incidence of lung cancer (OR, 0.75 [95% CI, 0.58-0.95]; 2 RCTs [n=36 052]; ARD, 0.2%). [21]

Randomized trials could not detect any benefit of supplementation with vitamin D, alone or in combination with calcium, on cancer risk at either high or low doses despite some evidence showing reduction in gross cancer mortality. [22,23,24] In a recent study, Zhang and coworkers observed that vitamin D deficiency aggravated growth and metastasis of prostate cancer in nude mice and transgenic adenocarcinoma of the mouse prostate (TRAMP) mice possibly through promoting epithelial mesenchymal transition (EMT) in two β-catenin-related mechanisms.[25] A trial conducted on prevention of cancer using vitamin E and selenium demonstrated that supplementation with vitamin E (400 IU/day) led to a 17% increase in prostate cancer risk among men.[26] Maternal folic acid supplementation is reported to lower the risk of neural tube defects. However, high supplementation with folic acid may assist cancer progression, especially in countries doing mandatory fortification with folic acid.[27] Most notably, Cole and coworkers have suggested that supplementation with folic acid at ≥1 mg/day may assist the growth of undiagnosed colorectal adenomas.[28] However, a meta-analysis of eleven randomized trials conducted on fifty thousand individuals demonstrated that the folic acid supplementation had no effect on site-specific cancer risk within the first five years of treatment.[23]

More recently, Mohseni and coworkers have published a review paper on trials conducted for effect of vitamin C and vitamin E on cancer survival.[29] They have covered thirty trials conducted on 38936 patients with different cancers. Although their study supported improvement of survival and progression rates of cancers by vitamins C/E they advocated more high-quality trials with large sample size to confirm their results.

2.3 Effect on type-2 diabetes

A major risk factor for type 2 diabetes mellitus is diet. Some investigations carried out on the use of supplements such as vitamins C, E, and β-carotene in reducing the risk of type 2 diabetes are reported in literature. These studies didn't find any effect of these supple-

ments in reducing type-2 diabetes.[30,31] A recent placebo-controlled trial of vitamin D supplementation (4000 IU/day) led to an increase in the serum hydroxyvitamin D concentrations significantly but failed to lower the risk of type 2 diabetes.[32]

A review article published by Valdes-Ramos, et al. mentions that the absorption of folic acid and vitamin B_{12} is reduced by the prolonged use of metformin. Metformin is a biguanide and well known first line drug in management of uncomplicated type 2 diabetes. Thus, people taking metformin for longer time were found deficient in folic acid and vitamin B_{12}. Such people need to be administered folic acid and vitamin B_{12} regularly.[33]

Vitamins and minerals are well known to improve the glucose metabolism because they are cofactors essential for enzyme functions. Kimball and coworkers have studied the effects of a nutrient intervention program on diabetes status.[34] The study revealed that vitamin D combined with other nutrients led to a lowered risk of progression to diabetes and an enhanced rate of reversion to normoglycemia in high-risk people. The results further suggested that the nutrient supplementation regimes may offer a safe, cheaper and effective means for bringing down the risk of diabetes. However, they suggested further evaluation of this potential using randomized controlled trials.

2.4 Effect on immune system

The immune system constitutes a large network of different organs, cells, and proteins. Its function is to protect the body from harmful microorganisms such as bacteria, fungi, and viruses, and toxins (harmful chemicals produced by microbes). Vitamins are long known to influence immune system. The vitamins A, C, D, E, B_6, B_{12}, and folate, and minerals like copper, iron and zinc play role in immune system response. Even small deficiency of one of these vitamins or minerals may result into impaired immune response.[35] During the last decade, vitamins A and D received particular attention because these vitamins showed unexpected and crucial effects on immune response. Mora et al. have mentioned in their review article that the metabolites of vitamins A and D retinoic acid and $1,25(OH)_2VD_3$, respectively, were capable of binding to nuclear receptors and exerting potential and specific immunomodulatory effects.[36]

Vitamin and mineral deficiencies are more common in older people that may lead to age-related weaker immune system response. Several studies suggested that supplementation with multi-vitamin and mineral supplements could improve the function of immune system in people aged 55 years and above. This hypothesis has been tested recently by Fantacone and coworkers by a double-blind randomized controlled trial.[37] They administered healthy older people with either a multivitamin and multimineral (MVM) combination formulated to improve immune response (Redoxonfi VI, Singapore) or an identical, inactive placebo control to take daily for 12 weeks. The group measured their (a) blood mineral and vitamin status (i.e., vitamin C, zinc and vitamin D), (b) immune status (salivary IgA and plasma cytokine/chemokine levels), (c) immune function (i.e., whole blood bacterial killing activity, neutrophil phagocytic activity, and reactive oxygen species production), and (d) self-reported health status, before and after treatment. The MVM supplementation led to an increase in vitamin C and zinc levels in blood and self-reported health-condition without changing measures of immune function or status of vitamin D levels, indicating that healthy older people might benefit from multivitamin and mineral supplementation.

2.5 Effect on HIV/AIDS

At the beginning of the 21st century approximately forty million people across the globe were infected with HIV and many of them had symptoms of AIDS. People with HIV infection were found deficient in micronutrients particularly in low-income settings probably because their diet was not balanced and deficient in essential vitamins and minerals. Early studies had suggested supplementation with micronutrients as cost-effective immunomodulator intervention that might slow the progression of HIV. Some studies had found that women with HIV infection who took a daily multivitamin were about half as likely to go on to develop AIDS as those who didn't take one. These early findings were reviewed by Singhal and Austin.[38] The vitamin that researchers investigated included vitamins A, B, C, and E. In 2004, Fawzi and coworkers conducted study on 1078 preg-

nant women infected with HIV in Dar es Salaam, Tanzania. This group used a double-blind, placebo-controlled trial, to study the effects of daily supplementation with vitamin A (preformed vitamin A and β-carotene), multivitamins (vitamins B, C, and E), or a combination of both to assess the progression of HIV infection. The survival models were used for this study. Their study showed that the median follow-up regarding survival was five years and eleven months (interquartile range, 46 to 80). They recommended the use of these vitamins before initiating antiretroviral therapy in HIV-infected women.[39]

However, most of the multivitamin research was carried out before antiretroviral therapy (ART) became common. At present, ART is the only reliable therapy for HIV. Markham Heid in his article on WebMD.com writes that newer studies have revealed that, while safe, multivitamins don't have the same benefits among people taking ART or other similar drugs.[40]

Visser and coworkers recently published a study with an objective to assess the effectiveness and safe use of micronutrient supplementation in reducing mortality and HIV-related morbidity of HIV-positive adults (excluding pregnant women). They reviewed the research carried out in between 2010 and 2016 for new randomized controlled trials (RCTs) of micronutrient supplements.[41] RCTs that compared supplements containing either single, dual, or multiple micronutrients with placebo, no treatment, or other supplements were included.

A total of 33 trials in which 10, 325 people participated, were conducted. Of these, seventeen trials were new. Ten trials were conducted to compare a daily supplementation with multiple micronutrients to placebo in doses up to 20 times the dietary reference intake.[41] A trial was also conducted to compare a daily standard dose with a daily high dose of multivitamins. Nineteen trials were conducted to compare supplementation with single or dual micronutrients (e.g., vitamins A and D, zinc, and selenium) to placebo, and three trials were conducted to compare different dosages or combinations of micronutrients.[41]

The analyses of these trials did not reveal consistent clinically significant advantage of routine multiple micronutrient supplementation in people infected with HIV. However, the authors suggested that these findings should not be considered as a reason for not supplementing micronutrient to people infected with HIV, where specific deficiencies are observed or where the person's diet is not balanced healthy diet and does not supply the RDA of vitamins and minerals.

2.6 Effect on COVID-19

SARS-CoV-2, the virus identified for causing COVID-19 disease, was first reported to the WHO on 31st December 2019. COVID-19 was declared a global pandemic by the WHO on March 11, 2020.[42] There was consensus among medical practitioners to focus on strengthening the immune system of people. Vitamin C was the most prescribed vitamin whereas zinc was the most prescribed mineral.

Speakman et al. have published a review article recently with an objective to analyze clinical trials on the use of vitamins and supplements for the treatment of COVID-19 infections.[43] A total of seven research studies were selected for review. All selected research papers had evaluated the effect of vitamins and supplements for the treatment of COVID-19. Treatment included intravenous and oral administration of vitamin C, oral administration of vitamin D, , oral administration of vitamin D/magnesium/vitamin B_{12}, oral administration of zinc, oral administration of zinc/ascorbic acid combination, and intravenous administration of α-lipoic acid. There was variation in end points of each investigation, including the Sequential Organ Failure Assessment score, mortality, rate of intensive care unit (ICU) admissions, negativity of COVID-19 tests, oxygen requirements, and symptom burden. The study concluded that the vitamin D offered the most promising result among the vitamins and supplements used as it significantly decreased the oxygen requirements, SARS-CoV-2 RNA test positivity, need for ICU treatment, and mortality in hospitalized patients. Other vitamins and supplements that were investigated had no statistically significant advantage.

2.7 Effect on osteoporosis

Calcium and Vitamin D3 are well known supplements to be recommended for managing bone health. In Botswana, many orthopedics recommend 1000 mg/day cal-

cium intake in adults over 50 years of age. Vitamin D3 is recommended if the deficiency is diagnosed by blood test. Usually, a dose of 5000 μg/week for 3-6 months is recommended. However, the research findings on the role of vitamin D and calcium supplementation are inconsistent. A meta-analysis of trials in community of older adults revealed that vitamin D or calcium supplementation had no effect in lowering the risk of hip fracture or total fracture.[44]Another meta-analysis revealed that while vitamin D alone did not lower the risk of fracture, supplementation with a combination of calcium and vitamin D led to reduction in the relative risk of hip fracture by16% and of all fractures by 6% among older adults.[45]A recent three years trial of 400, 4000, or 10 000 IU vitamin D/day for three years on 311 healthy adults reported that the higher doses led to statistically significant lower radial bone mineral density, indicating potential for harm.[46] However, in the absence of conclusive evidence, it is important to take these supplements to maintain recommended levels.

3. Conclusion

In conclusion, vitamins and minerals are important supplements but not substitutes of the balanced healthy diet. Older people are at increasing risk of becoming vitamin deficient. The level of vitamins and minerals in such people should be monitored regularly and the minimum recommended levels of vitamins and minerals must be maintained. The results of different studies carried out on the potential of vitamins and minerals in treating or managing certain diseases are not very promising. Vitamins and minerals were observed to have almost no effect on cardiovascular diseases, diabetes, or cancer. Some studies showed that vitamins and minerals improved the functioning of immune system in older people. Earlier studies had indicated the potential of vitamins for treatment of HIV/AIDS but now the antiretroviral therapy is the most beneficial in managing HIV/AIDS. In case of osteoporosis, a meta-analysis led to conclude that the relative risk of hip fracture was decreased by 16% and of all fractures by 6% among elderly people supplemented with a combination of calcium and vitamin D. A higher dose of vitamin D has been indicated to cause potential harm. □

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