Areej Raed Aljohani et al, 2023;7(4):711–715.
https://doi.org/10.24911/IJMDC.51-1672572974

REVIEW ARTICLE

Micronutrients' toxicity from causes to adverse effects: a review

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ABSTRACT

Micronutrients are essential elements for a good health state. However, the use of micronutrient supplements is a double-edged sword. For instance, the toxicity of micronutrients may be fatal in many cases. Meanwhile, micronutrient supplements are commonly used among children and pregnant women. Therefore, knowledge about the safety burden of micronutrient use is necessary for preventing severe events for both subgroups. However, the available data regarding micronutrient toxicity are limited. In this review, we discussed the toxicity and the adverse events of common micronutrients due to excessive intake and misuse of micronutrient supplements.

Keywords: Micronutrients, toxicity, Vitamin D, Vitamin A, Iron.

Literature Search

This review of the literature was undertaken through the PubMed database. The search MESH terms were multiple combinations of "Micronutrients," "Vitamin D," "Vitamin A," "Iron," or "Toxicity." Micronutrients term is defined as substances consisting of vitamins and trace elements. Vitamins are organic substances divided into water-soluble (vitamin B, vitamin C, and folate) and fat-soluble vitamins (A, D, K, and E). Meanwhile, the trace elements are metals (selenium, iron, zinc, etc.) found in small quantities in the body. Both vitamins and trace elements are necessary for normal metabolism in the human body [1].

Importance of Micronutrients

Micronutrients such as vitamins A, B2, B6, B12, C, D, and E, folic acid, zinc, iron, and selenium are essential in strengthening the immune system [2]. Those micronutrients have antioxidant and immunomodulatory effects that impact a person's exposure to infectious diseases and the consequences of any infection [3]. Moreover, the deficiency of folic acid and zinc during pregnancy can lead to congenital malformations and pregnancy complications. Additionally, the lack of iron in the pregnant woman may result in anemia that increases the risk of death during delivery due to hemorrhage [4]. Iron, vitamin A, and zinc deficiency in children can result in anemia [5]. Athletes' adequate copper, magnesium, and zinc intake improve physical activity and performance [6].

Prevalence of Micronutrients Use

The use of micronutrient supplements dramatically increased in the past years [7]. Vitamins are often used without a physician's prescription. Most Americans use vitamin supplements with their regular medications, but only one-third inform their physicians about that use [8]. In Germany, around 20% were self-medicated with micronutrients [9]. Additionally, in developed countries, 20%-30% of the population uses multivitamin supplements [10].

Factors Associated with Self-Medication

Numerous social, economic, and psychological factors can affect the self-medication of micronutrients. Previous reports have shown a higher use rate among females, middle-aged adults, older people above 60, college graduates, people with a higher social status, people living alone, racial minorities, previous and non-smokers,

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Received: 01 January 2023| **Accepted:** 06 January 2023

athletes, and adults who were paying less for medical care [11]. Moreover, a survey was conducted in Pakistan among pharmacy students toward self-medication of micronutrients. The survey demonstrated that the leading cause of self-medication of micronutrients was good health or gaining energy. In addition, the study showed the harmful consequences of excessive intake of micronutrients [12]. Prior studies on the magnitude or the reasons for micronutrient use or self-medication are scarce in the Middle East and North Africa region and the gulf area.

Vitamins and Micronutrient Toxicity

Due to the excessive use of micronutrients, the abuse and toxicity of micronutrients were reported. The United Kingdom Food Standards Agency, reviewed about 36 minerals and vitamins to discuss the several adverse events that came from those micronutrient supplementations [13]. Additionally, the safety of high doses of micronutrients was reported by several reviews conducted by national and international systems in the European Union [14] and the United States [15]. In addition, the assessment of the safety of micronutrient doses has been reported by the International Program on Chemical Safety [16] and the Nordic Council [17]. The data associated with the effects of excessive intake of micronutrients were reported from several clinical studies on nutritional needs, the interaction between nutrients, clinical studies for medical use, anecdotal case reports, and epidemiological studies. Anecdotal case reports reported the abuse dosages but did not identify the incidence of adverse events of micronutrients. Clinical trials can report the adverse effects of therapeutic indications. However, that clinical trial reported the adverse effects of micronutrients at therapeutic doses that may be associated with substantial nutritional intake [1]. The toxicity of vitamins is mostly due to excessive intake of vitamin supplements that exceed the recommended dose or due to interaction with other drugs [18]. For example, the interaction between vitamin E and aspirin or warfarin increases the risk of bleeding [19].

Vitamin D toxicity

Vitamin D supplement use dramatically increased in recent years. Unfortunately, the intake of vitamin D by the general population may occur without medical consultation or monitoring, leading to exogenous hypervitaminosis D, known as vitamin D toxicity (VDT) [20]. VDT occurs due to the extended use of vitamin D or inappropriate administration of vitamin D supplements [20]. Meanwhile, abnormally high exposure to sunlight or eating more foods containing vitamin D does not result in that toxicity [20]. VDT is characterized by severe hypercalcemia, hypercalciuria, and very low or unrecognized parathyroid hormone activity [21]. VDT also had negative impacts on the cardiovascular system. For instance, VDT results in hypertension, ST-segment elevation, and shortened QT interval. In addition, VDT can mainly cause hypercalciuria, nephron-calcinosis, and renal failure [22]. Institute of Medicine reported that several studies demonstrated the serious adverse events of VTD, including fracture and incidence of cancers such as pancreatic, prostate, and breast cancer [23]. In addition, a study on older women demonstrated a higher risk of fractures and falls among those who received a high annual dose of vitamin D (500,000 IU) [24].

Vitamin A toxicity

Vitamin A is a fat-soluble vitamin not synthesized by the human body. Therefore, obtaining the required vitamin A from diet or vitamin A supplements is necessary [25]. Despite the rare occurrence of vitamin A toxicity, it can happen due to excessive intake of vitamin A either in oral or topical supplements [26]. Hypervitaminosis A is characterized by several symptoms, such as nausea, vomiting, blurred vision, hair loss, muscle pain, bleeding, and altered mental status [27,28]. Additionally, excessive intake of vitamin A results in intracranial hypertension, characterized by increased intracerebral pressure and confusion [29]. Vitamin A overdose in the form of retinoid is known as "retinoic acid syndrome." That syndrome is characterized by acute respiratory distress with pleural and pericardial effusions, dyspnea, fever, edema, and in severe cases, multiorgan failure [30]. Additionally, a cross-sectional study conducted in Sweden showed the association between excessive intake of vitamin A and osteoporosis and hip fracture [31]. Topical vitamin A is also found in the form of retinoid preparations. Topical retinoids may lead to several adverse events, such as erythema, temporal hypo or hyperpigmentation, and psoriasis [32].

Vitamin B6 toxicity

Vitamin B6 is found in the form of pyridoxine (PN) supplements. Several case reports demonstrated that excessive intake of PN supplements resulted in progressive sensory peripheral neuropathy. PN-induced neuropathy is characterized by paresthesia, bone pains, numbness, fasciculations, hyperesthesia, loss of tendon reflexes, and muscle weakness [33]. A study in the United States reported that the most prevalent cause of toxic neuropathy was the excessive intake of vitamin B [34].

Vitamin E toxicity

Vitamin E is a fat-soluble antioxidant and anti-inflammatory agent in some conditions, such as osteoporosis [35]. On the other hand, the excessive intake of vitamin E leads to an increase in the risk of bleeding [35]. Additionally, several medications such as aspirin, tamoxifen, cyclosporine, and warfarin interact with vitamin E leading to severe bleeding. Moreover, the toxicity of vitamin E may result in gastrointestinal

derangement, thrombophlebitis, tenderness of the breast, and thyroid disorder [35].

Iron toxicity

An iron supplement is essential in iron-deficient cases related to iron deficiency anemia, blood loss, chronic inflammatory disease, malabsorption, and nutrient deficiency. Iron supplements are administrated as oral or intravenous (IV) iron [36]. Both routes of administration have several adverse events. For instance, oral iron supplements adversely cause nausea, vomiting, constipation, epigastric distress, and teeth staining [37,38]. Meanwhile, IV iron supplements may cause anaphylaxis [39]. The toxicity of iron supplements depends on the dose of iron intake. The 20-60 mg/kg dose leads to moderate toxicity. Meanwhile, a dose over 60 mg/kg results in severe toxicity and mortality. The most common symptoms of iron toxicity are metabolic acidosis, seizures, hypoxia, tachycardia, arrhythmia, and acute metabolic encephalopathy. Additionally, an overdose of iron in children under 6 years can lead to fatal poisoning [40].

Zinc toxicity

Zinc is an essential micronutrient that plays a main role in DNA expression, vitamin A metabolism, and the olfactory and gustatory systems [41]. Additionally, zinc supplement plays a significant role in fetal growth and in treating Wilson's disease [42]. The toxicity of zinc overdose is common [43]. Zinc toxicity adversely causes dyspnea, potential GI bleeding, anemia, and lethargy [44]. Additionally, excessive zinc intake for a long time results in a higher risk of prostate cancer and improper copper metabolism leading to anemia [45].

Conclusion

This review provides a comprehensive view of micronutrient supplements' adverse events and toxicity. It illustrated that the balanced use of micronutrient supplements is essential to avoid both deficiency and toxicity of micronutrients. Further studies and reviews are recommended to demonstrate the prevalence of misuse and serious effects of the overuse of micronutrients, especially in subgroups such as children, pregnant, and the elderly.

List of Abbreviations

IV	Intravenous
PN	Pyridoxine
VDT	Vitamin D toxicity

Conflict of interest
Not applicable.

Funding
None.

Consent to participate
Not applicable.

Ethical approval
Not applicable.

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