

Hypervitaminosis - An Emerging Pathological Condition

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ABSTRACT

Vitamins are essential organic compounds that are required in small amounts to regulate various metabolic activities in the body. Prolonged and overconsumption of pharmaceutical forms of both water-soluble and fat-soluble vitamins may lead to toxicity and/or hypervitaminosis. Hypervitaminosis is an acute emerging pathological condition of the body due to excess accumulation of any of the vitamins. In case of acute poisoning with vitamin supplements/drugs, emergency assistance is required to detoxify the effects and restore the organization, structure and function of body's tissues and organs. Sometimes death may occur due to intoxication to liver, kidney and heart. So, to manage any type of hypervitaminosis, proper diagnosis is essential to initiate eliminating the cause of its occurrence and accelerate the elimination of the supplement from the body. The present review discusses the symptoms of hypervitaminosis that seems to be a matter of concern today and management strategies to overcome toxicity or hypervitaminosis.

Keywords: Hypervitaminosis, Toxicity, Vitamins, Vitamin pathology, Fat-soluble vitamin, Water-soluble vitamin.

INTRODUCTION

Vitamins are potent organic compounds present in small concentrations in various fruits and vegetables. They regulate physiological functions and help in maintaining metabolic rate of the body. The human body cannot synthesize vitamins on its own. Therefore, it becomes essential to obtain right and sufficient vitamins through the diet in order to maintain healthy lifestyle. Imbalanced and poor diet leads to deficiency of vitamins in the body. This may bring about outburst of various deficiency diseases which if untreated with adequate supplements may lead to death of an individual. Vitamins are broadly categorized into, fat-soluble vitamins and water-soluble vitamins. Vitamins A, D, E and K are fat-soluble vitamins. They are not lost by cooking and can be stored in the

body, particularly in the liver. Vitamin B Complex and vitamin C are water-soluble. They are dissolved easily in food during cooking and a portion of these vitamins may be destroyed by heating. They cannot be stored in body and hence they have to be taken daily in foods. Any extra quantity taken in one day is eliminated in urine as waste by the body.

Presently, vitamins are made in different formulations by various pharmaceutical companies in the form of syrups, tablets, pills and powders that are readily available to be taken as supplements. Therapeutic use of vitamin supplements in the form of vitamin therapy has helped people in fighting diseases and managing good health. Modern life style has created an epidemic of binge drinking, missing diets, irritability and indigestion. People are

trying to integrate healthy habits into already hectic schedule and to compensate for the loss of essential nutrients in the form of vitamins, people have started taking vitamin supplements daily, believing that in case of increased concentration, excess of the vitamins will be lost independently from the body. This misconception and prolonged intake of vitamins may cause toxic effects in the body or hypervitaminosis, although rare. Hypervitaminosis is a condition reported of having abnormally high storage levels of vitamins leading to toxic symptoms. Generally toxicity and hypervitaminosis is caused by a large intake of highly fortified foods which leads to accumulation of fat-soluble vitamins in the liver. Natural foods have not been associated with any toxicity. [1,2] In the United States, the annual report submitted by poison control centres reported that more than 60,000 people including children under the age of 6, were subjected to life threatening outcomes due to vitamin toxicities. [3-5] The Dietary Reference Intake recommendations from the United States Department of Agriculture define a "tolerable upper intake level" for most of the vitamins. [6]

Most of the natural fruits and vegetables are considered to be the potent source of antioxidants instead of the antioxidant supplements in the form of pills and tablets. Studies reported that in the well-nourished individuals, prolonged intake of the antioxidant supplements including vitamin A and vitamin E may cause increase in mortality as a result of unwanted consequences to the health. [7-9] Whereas, vitamin D3 supplements have been known to decrease mortality in elderly people who are living independently or in an institutional care. [10] It has been observed in trials that regular intake of vitamin C supplements reduce the duration of cold but this was not replicated when therapeutic trials were conducted. Regular intake of vitamin C supplements have not been reported to reduce the incidence of occurrence of cold in general population. [11]

GENERAL SYMPTOMS OF

HYPERVITAMINOSIS

Hypervitaminosis may be acute and chronic with very specific and general clinical symptoms. Acute hypervitaminosis is the result of one time intake of very high dose of one or multiple vitamin preparations/supplements. Chronic hypervitaminosis results due to gradual development of clinical symptoms by a latent course. Water-soluble and fat-soluble vitamin toxicity has their own specific effects on the body leading to intoxication syndrome. Certain symptoms of intoxication syndrome are common to all the forms of hypervitaminosis like headache, severe weakness, dizziness, inability to exercise, inability to perform daily routine, nausea, sensations of internal tremor, constipation or diarrhoea. Hypervitaminosis due to fat-soluble vitamin groups have a more pronounced course as these get accumulated in the body tissues and cause severe intoxication. Hypervitaminosis due to water-soluble vitamins has a less pronounced course and does not impose a threat to the life of a person. Therefore, it can be normalized by increasing the urinary output and restricting the intake of such type of supplements.

HYPERVITAMINOSIS OF DIFFERENT VITAMIN TYPES

HYPERVITAMINOSIS A-- It occurs due to prolonged uncontrolled ingestion of too much of preformed vitamin A from foods (fish oil, animal liver and kidney, plant sources like carrots), supplements in the form of pills/ tablets/ powders or prescription medications. Dietary vitamin A is available mainly as preformed vitamin A in western countries and as provitamin A carotenoids in developing countries. Vitamin A in supplements per capsule is typically 10,000-50,000 international units (IU). Fish-liver oils may contain more than 180,000 IU/g. The acute toxic dose of vitamin A is 25,000 IU/kg, whereas the chronic toxic dose is 4000 IU/kg every day for 6-15 months. [12]

Hypervitaminosis A may be acute or chronic. An acute form is extremely rare and the symptoms may express as headache, vomiting, short-term loss of consciousness, dizziness, irritability, nausea, abdominal pain, fever, skin rashes without clear localization all over the body and visual disturbances like diplopia. The chronic forms are associated with the symptoms like dry patchy skin, dry fissured lips, hair loss and brittle nails. It affects the osteoarticular apparatus by altering bone metabolism accompanied by stiffness in movements, pain and swelling of periarticular soft tissues. It is also accompanied by anorexia (over eating may result in irreversible health complications including death), alopecia (baldness), weight loss, low grade fever, hepatosplenomegaly, papilloedema (optic disc swelling caused by increased intracranial pressure due to any cause), pseudotumor cerebri (caused by increased pressure around the brain). Other features include complications like hypercholesterolemia and atherosclerotic disease, anemia and thrombocytopenia (in infants), ^[13] hypocalcaemia, hypercalciuria and renal stones, benign intracranial hypertension and increased production of mineralocorticoids leading to generalized edematous syndrome, depression and suicidal tendencies (particularly with isotretinoin). ^[14,15] In pregnant women, long-term use may cause severe teratogenic effects in fetus including malformations of eyes, skull, lungs and heart. ^[15] In elderly persons the symptoms may manifest in the form of worsening of all the pathological conditions, decreased vision, imbalance of lipidogram indices, arrhythmia (irregular heartbeat), common arthralgia (pain in joints), chronic hepatic and renal failure. Hypervitaminosis A affects skin predominantly. ^[16]

No toxicity has been associated with the use of large doses of supplements of beta-carotene as compared with preformed vitamin A. But carotenoderma (harmless condition in which skin turns yellow-orange) has been reported by long term

intake of beta-carotene in men. ^[17] This can be reversed by discontinuing the intake of beta-carotene. Toxicity due to vitamin supplements has also been reported in children. ^[18]

Management is by discontinuation of supplements and taking prescribed recommended dose. If mental changes are reported, hospitalization is required. Once identified, the prognosis is good. Mortality is rare. Yellow colour of skin gets reversed with time.

HYPERVITAMINOSIS D-- It is caused by prolonged and/or excessive intake of prescribed medications such as calcium along with vitamin D. Excessive exposure to sunlight does not result in excessive levels of vitamin D. Today people tend to stay indoors and this concern about vitamin D deficiency that has led to the increased/over consumption of various forms of vitamin D supplements. The acute toxic dose for vitamin D has not been reported. The chronic toxic dose in adults is higher than 50,000 IU/day. In infants younger than 6 months, 1000 IU/day may be considered unsafe. The tolerable upper intake level (UL) for all groups > 1 year is 2000IU/day. ^[19] Therefore, there is wide variation in the potential toxicity for vitamin D. Toxicity is much more likely to occur from high intakes of dietary supplements containing vitamin D. Long term intakes above UL increases the risk of adverse side effects. ^[20] Hypervitaminosis D is occasionally associated with increased production of calcitriol as in hyperparathyroidism. Secondary hypercalcaemia is noticed with increased bone resorption and hypercalciuria along with polyuria, polydipsia, vomiting, dehydration, constipation, anorexia and lethargy, hypertension, tetany and seizures that may be fatal. ^[21]

In adults, hypervitaminosis D results in muscle weakness, frequent and rapid fatigue, functional dyspepsia (indigestion), sub febrile type of fever, with progressive weight loss, constant headaches without clear localization, hypertensive

crises leading to stroke, development of various forms of cardiomyopathies [22] accompanied with bradyarrhythmic disorders of cardiac activity and generalized icterus of the skin and mucous membranes. Signs of acute poisoning include tremors of distal parts of the extremities, a sharp pain syndrome in the muscles of back and extremities, general dehydration of the body and subcutaneous hemorrhages of various forms and to different extent. The uses of supplements of both calcium and vitamin D by post-menopausal women have known to cause risk of kidney stones. [23] In pregnant women, there is the risk for the development of bone structure anomalies. Certain nonspecific symptoms have been associated with vitamin D toxicity such as weight loss, anorexia, polyuria, heart arrhythmias, raised blood calcium leading to stones in urinary tract, vascular and tissue calcification that may cause damage to the heart. Long-term high-dose supplement intake may result in adverse health effects, increase in mortality, greater risk of pancreatic cancer, cardiovascular events, more falls and fractures in elderly. Hypervitaminosis has also been recognized as a cause of depression. [24] In children it has been associated with dental enamel hypoplasia and focal pulp calcification. [25] Complications may arise due to increase in serum calcium levels, cardiac enzyme elevations, disturbances in renal function tests leading to chronic kidney disease, nephrolithiasis, nephrocalcinosis, calcinosis of the joints and periarticular tissues. [26]

Management is by discontinuing the supplements and treats the cause. In case of severe vitamin D intoxication, glucocorticoids are occasionally used for a short while. Bisphosphonates like pamidronate may be used to treat hypercalcaemia. Phenobarbital and phenytoin are used to prevent and control epileptic seizures, increase the hepatic metabolism of vitamin D to inactive compounds and reduce calcium absorption. [27] Both weight-loss drug orlistat and cholesterol-lowering drug cholestyramine

can be taken to reduce the absorption of vitamin D and other fat-soluble vitamins. [28,29] Short term toxicity can be ameliorated by administration of vitamins A and K. [26] The modulation of toxic effects of vitamin D3 by administering vitamin K may be due to biological activity of vitamin K dependent proteins that are synthesized in the liver and secreted into blood where they depend on the normal complement of Gla-residues that are efficient chelators of calcium ions and counteract hypercalcemia. [30] The protective effect of vitamin A in hypervitaminosis D3 is its ability to downregulate matrix Gla proteins in the soft tissues and prevents calcification in renal tissue. [31]

HYPERVITAMINOSIS E-- Naturally vitamin E is present in vegetable oils, unprocessed cereal grains, nuts and seeds. No adverse side effects have been reported after consuming vitamin E in natural foods. Today, people have started taking vitamin E supplements on a regular basis, because of its known antioxidant, [32] antiatherogenic, [33] fertility promoting (anti-sterility) [34] and anti-ageing [35] properties. The recommended daily dose is 3- 25 mg/day and the side effects are observed at doses above 1g/kg. Physicians have reported few cases of cerebral haemorrhage due to prolonged intake of vitamin E at a dose of 50 mg/day. Healthy individuals taking vitamin E daily at a dose of 100mg or more for prolonged duration (one year) are likely to exhibit hypervitaminosis E. High daily dose @ 150-200 mg/ kg body weight / day may result in cystic fibrosis abetalipoproteinemia. The number and severity of side effects are directly proportional to the dose and duration of vitamin E intake. Increases in all-cause mortality have been reported after consuming large overdose of vitamin E supplements. [9,10,36] High doses of alpha-tocopherol supplements can affect blood clotting by inhibiting vitamin K-dependent carboxylase and thus leads to increased bleeding, inhibit platelet aggregation by reducing the platelet thromboxane

production, cause haemorrhage and can impair immune system by decreasing phagocyte activity of leucocytes, leading to necrotic enter-colitis, neuromuscular and endocrine disturbances. [37,38] The cardiovascular effects associated with hypervitaminosis E are aggravation of angina, hypertension, acceleration of atherogenesis, and restenosis process and reduction of cerebral blood flow leading to stroke. [36, 39] Certain dermatological, renal and gynecological side effects have also been reported, like ecchymosis and chapping of lips, creatinuria and creatinaemia, irregular vaginal bleeding, gynaecomastia, breast cancer and disturbances in reproduction. [38] Fatigue, weakness, headache and gastrointestinal disturbance, diarrhoea, intestinal cramps and delayed wound healing have also been associated with vitamin E toxicity.

Management is by discontinuing the supplements and treats the cause. Try to consume daily recommended dose only. **HYPERVITAMINOSIS K--** Vitamin K1 and vitamin K2 are the two common forms of vitamin K. Vitamin K1 is produced in green leafy vegetables like turnip, spinach, cauliflower, cabbage, broccoli and Brussels sprouts and also found in cow's milk, soy oil, cottonseed oil, canola oil and olive oil. Vitamin K2 is synthesized by intestinal bacteria in the body. Both the forms are likely safe for most people when taken by mouth or injected into the vein. Side effects are negligible in most people who prefer physician's recommended amount each day. There isn't enough scientific information to determine recommended dietary allowances for vitamin K. It has been reported that if one is suffering from diabetes, monitoring of blood sugar level becomes necessary as vitamin K1 might lower blood sugar level. High doses of vitamin K can worsen the clotting problems caused by severe liver disease. Vitamin K toxicity can occur only with type K3 that leads to haemolytic anemia by inhibiting the glutathione function that may lead to accumulation of reactive oxygen species. This may cause

rupture of RBC membrane due to oxidative stress and thus lead to haemolytic anemia, jaundice and liver damage. This is rarely observed in adults and is mostly seen in infants. People taking blood thinning drugs or anticoagulants should limit their intake of foods with vitamin K, as excess vitamin K can alter blood clotting times. [40,41]

HYPERVITAMINOSIS C-- The acute toxic dose for vitamin C has not been determined. The chronic toxic dose is more than 2 g/day. The maximum dose for adults should not exceed 90 mg/day. The symptoms of hypervitaminosis C in adults are manifested in general as feeling of weakness, dizziness, diarrhoea, nausea and vomiting, insomnia, strong headache, allergic reactions to skin, heartburn and stomach ache. Overdose of ascorbic acid have been reported to be associated with increased nervous excitability, unmotivated aggression, itching and rashes on the skin in children. Various serious consequences have also been reported with prolonged overdose of the supplement like kidney disease, gastritis and stomach ulcer, deficiency of vitamin B complex, disturbance of pancreas, increased blood pressure, clotting disorder, progressive deterioration of vision, disturbance in menstrual cycle (dysmenorrhea), change in morphological composition of the blood with the decrease in the number of leucocytes and hormonal disorders. Excessive amount of vitamin C in the body stimulates the accumulation of oxalates and their deposition in the renal tissue and gall bladder. [42] An overdose of vitamin C during pregnancy can cause severe disorders in the metabolism of the foetus. So, with extreme caution, ascorbic acid should be taken during pregnancy, diabetes, cataracts and impaired renal activity.

Management is by discontinuing the supplement use and increasing the urinary output.

HYPERVITAMINOSIS B COMPLEX-- Hypervitaminosis of group vitamin B complex has combined characters and the symptoms appear in the form of generalized

hyperemia and hypersensitivity of skin, headache of varying degrees of intensity without limited localization, intestinal ulcers, occurrence of sleep disorders, increased convulsive readiness, fatty liver, hyperglycemia, hyperuricaemia, nausea and indigestion are found. [42]

Hypervitaminosis B12 occurs in the elderly who take it in the parenteral dosage for more orally for treating malignant anemia. Overdose may lead to various types of allergic reactions, congestive heart failure, pulmonary oedema, reduction in the size of vascular controlled reflexes, palpitation, tingling sensation and numbness of limbs. The toxic dose for vitamin B12 has not been specified. The symptoms of hypervitaminosis B9 (folic acid) are specified by tonic convulsions in the gastrocnemius muscles that may occur at any time of the day and inhibition of the function of hepatic alcohol dehydrogenase. Sleep, stomach and skin problems are also associated with overdose. Side effects from an overdose of biotin (vitamin H/B7) are rare, as it is easily excreted in urine and faeces. Sometimes overdose may cause hyperkeratosis of superficial follicular epithelium. Hypervitaminosis B6 (Pyridoxine) is extremely rare. For its development the dose of the drug should exceed 1000times. Prolonged use of supplements at a dose of 300-500mg/day can cause severe and progressive sensory neuropathy with ataxia, painful skin rashes, photosensitivity, nausea and heartburn. [9, 10, 43]

The severity of symptoms is dose dependent. Excessive doses cause damage to sensory neurons resulting in paraesthesia in the hands and feet, difficulty in walking, tiredness, and reduced sensation to touch, temperature and vibration. Discontinuing the usage of vitamin B6 may resolve symptoms unless irreversible damage has occurred to neurons. Overdose of hypervitaminosis B5 (Pantothenic acid) may cause diarrhoea, gastrointestinal problems, and water retention leading to oedema. Hypervitaminosis B3 (Niacin) have not been established. However, some of the

adverse effects such as skin flushing have been reported at a dose of 50 mg/day or greater. The therapeutic doses are considered to range from 1,500-1,600 mg/day. Prolonged usage at a dose of 3 gm/day may be associated with risk for liver toxicity, low blood pressure, light headedness, insomnia, peptic ulcer, skin rash, hyperemia of skin, pruritus, gastrointestinal disturbances, aggravation of bronchial asthma, gout and fasting hyperglycemia. Hypervitaminosis B2 (Riboflavin) may result in liver dysfunction, photophobia, zaeda in the corners of mouth and cardiomyopathies, vomiting, itching, numbness, burning or prickling sensation, hypotension, fatigue and production of bright yellow urine. Overdose of Thiamine (B1) blocks nerve transmission, cause paralysis, restlessness, convulsions, respiratory paralysis and cardiac failure. It also interferes with other B vitamins, insulin and thyroid functions. [42]

DISCUSSION

Due to stress and hectic life style, the city dwellers are more prone to overeating or no eating at all. This has led to the loss or deficiency of vitamins in the body. To compensate for the imbalance or deficiency of essential vitamins needed for maintaining the basal metabolic activities, people have now-a-days started taking various vitamin supplements in the form of powders, syrups, tablets and pills without consulting and proper monitoring by the nutritionists and dieticians. This has led to accumulation of vitamins in the body tissues and fluids that cause toxicity/hypervitaminosis in the body. Toxicity/hypervitaminosis due to water soluble vitamins do not impose threat to the life of a person. Whereas, accumulation of fat soluble vitamins A,D,E and K may cause intoxication syndrome resulting in certain common symptoms like headache, inability to exercise and perform daily routine activities, diarrhoea, vomiting, constipation, irritability, nausea, weakness and dizziness. Hypervitaminosis can be normalized by

increasing the urinary output and limiting the intake of vitamin supplements. It is recommended to take the advice of the physician/nutritionist before taking vitamin supplements in different forms.

CONCLUSION

To avoid the signs of toxicity and/or hypervitaminosis, experts recommend restricting the use of pharmaceutical form of vitamins without consulting dieticians and gastroenterologists.

Conflict Of Interest – None

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