

VITAMIN SUPPLEMENTATION IN DISEASE PREVENTION

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SUMMARY – Vitamins are chemically unrelated organic compounds or families of organic compounds that are essential for normal metabolism in humans. As vitamins cannot be synthesized by a human body, they have to be taken in small amounts in the diet to prevent metabolic disorders. Vitamins should be distinguished from other ‘food supplements’, minerals and herbs, which are also taken in small amounts as alternatives or supplements to drugs. Mild deficiencies in several vitamins, at levels below those causing classic vitamin deficiency syndromes (e.g., scurvy or pellagra) are risk factors for chronic degenerative diseases such as atherosclerosis, cancer, and osteoporosis. Data on vitamin supplementation to prevent chronic diseases are reviewed.

Key words: *Vitamins – administration and dosage; Dietary supplements; Nutrition policy; Chronic diseases – prevention and control*

Vitamin Deficiency

The definition of vitamin deficiency has evolved since vitamins were first discovered. Gross vitamin deficiency may be recognized by obvious clinical syndromes. These syndromes are still seen in areas of the world with very poor diets. In the Western societies, they occur only in special populations, including the elderly, patients with alcoholism, malabsorption, and inborn errors of metabolism, and those undergoing hemodialysis or receiving parenteral nutrition.

The recommended daily allowances (RDAs) are the amounts necessary to prevent gross deficiency syndromes. However, these levels may not be adequate to prevent chronic disease in some people. Measurement of serum levels of several vitamins is now commercially available. They are useful if clearly very high or very low to diagnose or rule out gross deficiency. The intake or serum levels of vitamins have recently been related to biochemical abnormalities.

A new concept concerning adequacy of vitamin intake includes optimal daily ingestion of vitamins to prevent chronic diseases (e.g., vitamin D supplementation to prevent osteoporotic fractures, and folic acid to prevent neural tube defects). The remainder of this paper will address these preventive issues.

Folic Acid

Folate is present in green, leafy vegetables, fruits, cereals and grains, nuts, and meats. Folic acid, the form of the vitamin included in supplements, has the same biologic effects as folate but has higher bioavailability and therefore better dose for dose effectiveness¹. Gross deficiency in folic acid leads to megaloblastic anemia.

Pregnancy

Folic acid supplementation reduces the risk of neural tube defects, probably because it is required for normal cell division. Neural tube defects occur between postconception days 15 and 28². Thus, folic acid must be taken at the time of conception, since the neural tube has already been formed, or malformed, by the time that pregnancy is apparent.

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Folic acid supplementation is important not only in the early stages of pregnancy but throughout pregnancy. One study suggests that the lack of folic acid supplementation is associated with an increased risk of late fetal loss (intrauterine death at >22 weeks)³. Also, folic acid requirements increase during pregnancy, and its supplementation prevents maternal anemia.

Recommendations

The optimal dose of folic acid to prevent as many neural tube defects as possible is not precisely known. It is at least 400 micrograms/day, and may be as high as 800 micrograms/day, i.e. twofold RDA. A supplement of 800 micrograms is appropriate for women trying to conceive.

Homocysteine

Cardiovascular disease

Homocysteine is a major risk factor for vascular disease, including atherosclerosis (with resulting cerebrovascular, peripheral vascular, and coronary heart disease) and venous thromboembolism⁴. The relative risk associated with homocysteinemia is similar to cigarette smoking or elevated serum cholesterol⁴. Homocysteine has primary atherogenic and prothrombotic properties that may explain the increased risk of vascular disease.

Folic acid and vitamins B6 and B12 are required for the metabolism of homocysteine to methionine. A multicenter case-control study from Europe including 750 patients (mean age 47) with documented vascular disease and 800 control subjects (mean age 44) has reported that low levels of folate and vitamin B6 but not vitamin B12 were associated with an increased risk of atherosclerosis, independent of conventional risk factors⁵. The risk associated with folate was in part explained by increased homocysteine levels, whereas the relationship between vitamin B6 and atherosclerosis was independent of homocysteine levels both before and after methionine load.

The Nurses' Health Study found a graded inverse association between higher dietary intakes of folate and vitamin B6 and coronary heart disease (CHD)⁶.

Deficiency states of either vitamin B6 or B12 result in high plasma homocysteine levels. Differences in B12 absorption may be more important than dietary intake. These data suggest that suboptimal B12 intake coupled with poorer absorption might play a greater role in elevating homocysteine and subsequent CHD risk in the elderly than in younger patients. In contrast, a folate intake low

enough to raise plasma homocysteine may be relatively common in the general population, particularly in moderate consumers of alcohol.

Supplementation of both vitamin B6 and folate reduces homocysteine levels. Vitamin B6 may be more effective in counteracting the effects of methionine load (simulating the fed state) on homocysteine levels, whereas folate may be more important in regulating plasma homocysteine in the fasting state⁷.

Recommendations

In normal individuals and in patients with hyperhomocyst(e)inemia, folic acid would lower homocysteine by 25% and B12 by another 7% on an average, whereas B6 will not induce any additional lowering⁸. However, the effect of homocysteine level lowering on cardiovascular and venous thromboembolic disease remains unknown. No randomized clinical trials have demonstrated that decreasing plasma homocysteine levels reduces the incidence of cardiovascular disease⁹.

Until the results of appropriate trials are available, it is reasonable to recommend that adults at an average risk of cardiovascular disease take a folate supplement of 400 micrograms *per* day (twofold RDA), vitamin B6 supplement of 3 micrograms *per* day (150% of RDA), and vitamin B12 supplement of 9 micrograms *per* day (150% of RDA) because of the high prevalence of suboptimal vitamin B intake (especially in the elderly), insufficient dietary folate, and elevated homocysteine levels.

Cancer

Folate plays a key role in methionine regeneration. Folate deficiency may contribute to aberrant DNA synthesis and carcinogenesis by decreasing methionine availability and interfering with normal DNA methylation. A functional polymorphism in methylenetetrahydrofolate reductase (MTHFR, a major enzyme involved in folate metabolism), is linked to colorectal cancer¹⁰. Folate may therefore act to protect DNA against damage during cell division¹¹.

Recommendations

Folic acid appears to lower the risk of both colon and breast cancer, particularly in alcohol consumers. It is recommended that adults at an average risk of these cancers take a folate supplement of 400 micrograms *per* day. Although data on the appropriate dose are limited, moderate users of alcohol might benefit from additional folate

(800 micrograms *per day*), particularly those with poor intake of green, leafy vegetables or other food sources of folate.

Antioxidant Vitamins

The antioxidant vitamins include total vitamin A, consisting of preformed vitamin A (retinol), and the carotenoids such as beta-carotene, C and E. Countless other compounds found in food, especially vegetables and fruits, also have antioxidant properties. A number of studies have examined the hypothesis that antioxidants can prevent cancer and cardiovascular disease by augmenting the body's ability to dispose of toxic free radicals, thereby retarding oxidative damage¹². Retinol and the carotenoids may also decrease cancer risk *via* other mechanisms such as inducing cellular differentiation, apart from of protecting against oxidative damage.

Caution is warranted on interpreting the results of observational studies; while these have consistently shown that diets high in vegetables and fruits (which are rich in antioxidant vitamins) are associated with a reduced risk of cancer and cardiovascular disease¹³, the effect may be due to the vitamins themselves, other compounds in vegetables and fruits such as flavonoids, or substitution of dietary meat and fat with vegetables and fruits. Furthermore, while antioxidants are often grouped, specific antioxidant vitamins (including different forms of some vitamins) might be expected to have distinct effects. Individual responses may vary based upon genetic predisposition and other exposures including smoking, dose, and tissue of interest.

Vitamin A and Carotenoids

Cancer

Studies of the relationships between cancer and vitamin A and carotenoids have provided mixed results. Observational data and clinical trial data have not been consistent, limiting our ability to make conclusive recommendations.

Two large randomized placebo-controlled trials assessed the risk of lung cancer among male smokers or asbestos workers receiving beta-carotene supplements¹³. Both showed significant increases in lung cancer risk among men who received the supplements.

No clinical trial data are available on the associations between breast cancer and vitamin A and carotenoids, and observational studies have yielded varying results. In the

Iowa Womens' Health Study, no association was observed between dietary vitamin A and breast cancer¹⁴. In contrast, a weak but statistically significant 15% reduction in breast cancer risk was observed with high intake of total vitamin A in the Nurses' Health Study¹⁵. More recent data from the Nurses' Health Study suggest that premenopausal women, particularly those with a positive family history, have significant reductions in breast cancer risk with increasing dietary alpha- and beta-carotene, lutein/zeaxanthin, and total vitamin A¹⁶.

Data from a four-year clinical trial of antioxidants to prevent colorectal adenoma were also disappointing¹⁷. The Polyp Prevention Study Group reported no reduction in adenoma risk in 864 patients randomized to receive beta-carotene (25 mg daily), vitamin C (1 g daily) and E (400 mg daily), or both beta-carotene and vitamins C and E.

Possible explanations for discordance between observational data and experimental data with regard to vitamin A and carotenoids and cancer risk include the inability of observational data to completely control for confounding by other healthy behaviors, differences in the form or dose of vitamins, and interaction with other exposures such as tobacco. The clear increase in the risk of lung cancer in two randomized controlled trials has dampened enthusiasm for further clinical trials of cancer and antioxidants¹⁸.

Cardiovascular disease

Agents in vascular tissue and inflammatory cells are responsible for the oxidative modification of low-density lipoprotein (LDL), which is thought to play an important role in the pathogenesis of atherosclerosis. It has been hoped that treatment with antioxidant vitamins will prevent or retard atherosclerosis.

However, beta-carotene was not effective for primary prevention in three randomized controlled studies¹⁹, and may be harmful in patients with known CHD²⁰. As an example, a report from the ATBC Cancer Prevention Study noted that in men with a prior history of myocardial infarction there were significantly more cardiac deaths in the group taking both 50 mg daily of vitamin E (alpha-tocopherol) and 20 mg of beta-carotene (relative risk 1.58), and in those taking beta-carotene alone (relative risk 1.75).

Immunity

Vitamin A appears to improve immunity in children living in developing countries. A meta-analysis of 12 controlled trials of vitamin A showed a 30% reduction in overall mortality, with a 61% reduction in mortality among hospitalized patients with measles. One United States study

of children with measles showed more severe illness in children with more depressed serum retinol levels. Vitamin A supplementation at the community level in developing countries is recommended by the World Health Organization, even in the absence of signs and symptoms of deficiency²¹.

Recommendations

Beta-carotene supplement use should be discouraged based upon its lack of clinical efficacy and possible adverse effects with respect to both cardiovascular and cancer risk.

A diet with at least five servings of fruits and vegetables *per* day is prudent and is likely to provide an optimal distribution of carotenoids and the best opportunity to prevent several common cancers without the risk of unintentional harm.

Vitamin E

Cancer

A number of studies have examined the effect of vitamin E on cancer prevention. The ATBC Cancer Prevention Study observed a 32% decrease in prostate cancer incidence and 41% decrease in prostate cancer mortality among subjects receiving 50 mg (75 IU) of alpha-tocopherol (vitamin E) compared with placebo²¹. In contrast, observational data from the Health Professionals Follow-up Study showed no association between vitamin E supplement use and all prostate cancers. The study did, however, show a 66% decrease in the risk of metastatic or fatal prostate cancer among smokers who consumed at least 100 IU of supplemental vitamin E daily²².

The second report from the ATBC study showed a significant 19% reduction in lung cancer risk associated with higher serum vitamin E levels. The risk reduction was greatest among men younger than age 60 and among patients with fewer years of cumulative smoking exposure.

Neither the Iowa Women's Health Study nor the Nurses' Health Study observed any association between breast cancer risk and vitamin E intake^{14,15}.

No reduction in colorectal polyps was observed among subjects randomized to receive vitamin E in the Polyp Prevention Study¹⁶.

Cardiovascular disease

Vitamin E may prevent atherosclerotic disease not only by its antioxidant effects but also by the inhibitory effects on smooth muscle proliferation and platelet adhesion²³.

Observational data have suggested a protective effect for vitamin E against the development of CHD.

In an 8-year follow-up of nearly 88,000 women aged 34 to 59, the Nurses' Health Study found that women who reported vitamin E intake in the top fifth of vitamin E intake had a relative risk of major coronary disease of 0.66 compared with women in the lowest fifth²⁴. The beneficial effect has been attributed to supplemental vitamin E, since women in the highest quintile were all supplement users; no effect was observed for women taking less than 100 IU daily. Women who took vitamin E supplements for short periods had little apparent benefit, but those who took them for more than two years had a relative risk of major coronary disease of 0.59 after adjustment for coronary risk factors and use of other antioxidant nutrients. Dietary intake of vitamin E alone (as opposed to supplements) had no impact upon the risk of CHD. Similar results were noted in a cohort of almost 40,000 male health professionals, again with protective effects limited to doses of 100 IU or more daily²⁵.

Several large clinical trials have also studied the effect of vitamin E supplements in patients with pre-existing CHD²³. However, differences in vitamin E dose in these studies have made comparisons difficult. Only one (CHAOS) has shown a significant beneficial effect for antioxidant vitamins. In this study, relatively large doses of vitamin E, 400 to 800 IU alpha-tocopherol daily (13 to 26 times RDA), reduced the one-year rate of nonfatal myocardial infarction in patients with known CHD by 80%, but did not improve cardiovascular mortality²⁶. In the ATBC trial, the largest trial completed, no association was observed between vitamin E at a dose of 50 mg (1 mg = 1.5 IU) daily and CHD mortality or angina. The results of GISSI trial and HOPE trial showed no difference between vitamin E (400 IU daily) and placebo after an average of 4.5 years²⁷.

Stroke

A report from the Health Professionals' Follow-up Study (including 43,738 men) showed no association between supplemental vitamin E (250 IU or more daily) and stroke risk.

Dementia

A longitudinal cohort study of Japanese-American men (a population at a high risk of stroke and vascular dementia) found that both vitamin E and C supplementation protected against the development of vascular dementia and improved cognitive function late in life²⁸. However, the study did not account for other causes of vascular demen-

tia that may be confounded with the reported vitamin use, making firm conclusions difficult.

Other studies found that antioxidant vitamins could slow the progression of Alzheimer's disease. As an example, a randomized trial of selegiline, vitamin E, both, or placebo in patients with Alzheimer's disease showed that both selegiline and vitamin E were independently associated with significant reductions in several outcomes, including functional decline²⁹. The dose of vitamin E was quite high (2000 IU daily), and the study unfortunately suffered from imbalance in baseline characteristics after randomization. Nevertheless, based upon the current understanding of the pathophysiology of dementia, there is interest in confirmation of vitamin E effects in further studies³⁰.

Recommendations

Limited data support supplementation with vitamin E to prevent aggressive prostate cancer and lung cancer in smokers.

The amount of vitamin E generally available in a multivitamin (30 IU) appears to be ineffective for preventing CHD events; an additional supplement of 400 IU daily would be required. Individuals taking anticoagulants should be advised against high doses of vitamin E (4000 IU or more) because of the synergistic action of vitamin E with these drugs.

Vitamin C

Cardiovascular disease

A number of epidemiologic studies evaluated supplemental vitamin C intake for the primary prevention of CHD. The results were conflicting as both evidence of benefit and no effect on CHD risk were recorded. The role of vitamin C in patients with known CHD has not been thoroughly studied, however, the existing data do not support its use³¹.

Cataract and macular degeneration

Oxidative damage from sunlight and smoking increase the risk of cataract formation and macular degeneration. Growing evidence suggest that antioxidants prevent cataract development. Prospective data from the Nurses' Health Study showed a 45% reduction in the risk of cataract requiring extraction in women using vitamin C supplements for at least 10 years³². In another report from the same study, use of vitamin C supplements for at least 10

years was associated with a prevalence of early lens opacities lower by 77%³³. Multivitamin use and vitamin E supplementation were also associated with a decreased risk of cataract (30% and 55% risk reduction, respectively) in another observational study.

Recommendations

At the moment, there is no recommendation on taking vitamin C for the primary or secondary prevention of CHD, or for cancer prevention. Data are limited for supplemental vitamin C as a means of preventing cataract, limiting our ability to make recommendations at this time.

Vitamins B6 and B12 (Riboflavin)

Vitamin B6 (pyridoxine) participates with folic acid and B12 in the metabolism of homocysteine (see above). It has been difficult to separate out the effects of B6 from those of other vitamins and of other substances found in fruits and vegetables, and the optimal dose is not well characterized³⁴. However, as described above, vitamin B6 appears to be very effective in lowering homocysteine levels after methionine load, and is independently associated with lower CHD risk.

Although overt riboflavin deficiency is rare, one study showed the benefit of supplementation in preventing migraine³⁵.

Vitamin B12. Gross vitamin B12 deficiency causes neurologic disease and megaloblastic anemia. In addition, it is a cause of abnormal homocysteine metabolism, along with folic acid and vitamin B6 (see above); vitamin B12 deficiency is an important cause of hyperhomocysteinemia in the elderly³⁶.

Mild B12 deficiency, even without anemia, may account for some cases of dementia³⁷, and perhaps deteriorating balance in the elderly. This hypothesis is plausible although it has not been well studied.

Suboptimal vitamin B12 status is most commonly caused by poor absorption coupled with inadequate intake. In the elderly, gastric atrophy and hypochlorhydria result in less efficient absorption of vitamin B12 because of inadequate intrinsic factor; this modest decrease in absorption is likely to be by far more prevalent and important in vitamin B12 deficiency than the relatively rare condition of pernicious anemia. Patients with poor intake, including vegans, alcoholics, and people with little dietary variation (including the elderly) are also prone to B12 deficiency. Patients having undergone gastric or ileal resection have traditionally been treated with intramuscular vitamin B12,

since standard oral supplementation does not allow for adequate B12 absorption.

Recommendations

Routine supplementation with a multivitamin is appropriate for all adults. A supplement of 6 to 9 micrograms (100% to 150% of RDA) is recommended. In the elderly or other populations with a high prevalence of atrophic gastritis, vegan populations, alcoholics, and others with poor dietary variation, this dose may be inadequate. However, there are few data to guide dosing in these individuals; doubling the dose to 12 to 18 micrograms may be appropriate. There is no known toxicity of vitamin B12.

Toxicity of Vitamins

Potentially toxic levels of vitamins can be achieved easily in people who take large amounts of high-dose, over-the-counter preparations. Water soluble vitamins have an extraordinarily broad therapeutic ratio, with toxicity occurring only at doses thousands of times the RDA. It has been hypothesized that large doses of vitamin C may increase the risk of kidney stones by increasing oxalate excretion, but this remains controversial.

Fat soluble vitamins generally are also safer over a wide range of doses. A notable exception is vitamin A in pregnancy, which is teratogenic at doses as low as several times the RDA³⁸. As previously mentioned, the intake at which the dose of vitamin D becomes toxic is not clear, but is somewhere above 2000 IU *per day*.

Testing for Vitamin Deficiency

Blood tests for many vitamins are widely available. Fuelled by popular belief in the importance of vitamins and by commercial interests, widespread testing is being promoted to detect unrecognized deficiency and to tailor supplements to individual needs. This practice seems unwarranted in most patients for several reasons: 1) there is insufficient information about the optimal blood levels of vitamins, making it difficult to interpret mild deficiency states; 2) most people ingest too little of some vitamins such as folic acid; 3) a daily multivitamin is sufficient to reach optimal intake for most of the vitamin needs left uncovered by diets, and it is easier to take a multivitamin than to test for individual vitamin deficiencies; and 4) multivitamins are inexpensive and safe.

It may be that some individuals are at an unusual risk of vitamin deficiency and would benefit from special sup-

plements. As an example, an inherited abnormality of folic acid metabolism that causes unusually low serum levels of folic acid and increased levels of homocysteine has been identified in 5% to 15% of the population³⁹. However, this abnormality does not appear to be associated with an increased incidence of cardiovascular disease.

Additional information about polymorphisms, which increase requirements for specific vitamins, is likely to become available. As noted earlier, this appears to be the case for folate and vitamin D. However, there is currently not enough understanding of individual risk to warrant routine testing of vitamin levels or testing for polymorphisms.

Conclusions

Recommendations for the best use of vitamins are the following:

- A diet with five or more servings of vegetables and fruits *per day*. This diet promotes health not only by providing known vitamins, but also because it contains fiber and other poorly defined nutrients and replaces meat and animal fat.
- Women of childbearing age should take a vitamin supplement containing at least 400 micrograms of folic acid *per day*. Women who are trying to conceive are encouraged to take 800 micrograms of folic acid daily.
- Adults should take one multivitamin *per day*, mainly for the effect of folic acid (and vitamins B6 and B12) on homocysteine, of folate in reducing colon and breast cancer risk (particularly in alcohol users), of vitamin D on osteoporosis, and possibly of vitamin B12 on neurologic disease in the elderly.
- Discuss the possible benefit of vitamin E supplementation (400 IU) for patients with known cardiovascular disease. Discourage high doses for patients on anti-coagulants.
- Use of large doses of individual vitamins or multivitamins tailored to age, sex, or other medical conditions is not supported by strong research evidence.
- Use a generic form of 'one-a-day' multivitamin.
- Two multivitamins daily might be appropriate for some patients, particularly those with malabsorption, little dietary variation, and the elderly, or those with known osteoporosis.

Physicians should urge their patients to take the vitamins that are known to be effective while avoiding doses

that are toxic. They should also be interested in and non-judgmental about a wide range of behaviors between these extremes, so that patients will be willing to share their beliefs and information about the use of vitamins and other 'alternative' treatments.

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Sažetak

NADOMJEŠTANJE VITAMINA U PREVENCIJI BOLESTI

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Vitamini su tvari potrebne za normalan metabolizam čovjeka, a za njih je znakovito da se ne sintetiziraju u organizmu, nego ih u njega treba unijeti. Manjak određenih vitamina u organizmu čimbenik je rizika u nastanku nekih kroničnih degenerativnih bolesti, npr. ateroskleroze, karcinoma i osteoporoze. U članku su iznesene ključne spoznaje o značenju preventivnog unosa vitamina u organizam.

Ključne riječi: *Vitamini – primjena i doziranje; Dodaci prehrani; Način prehrane; Kronične bolesti – prevencija i kontrola*