Clinical Practice

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

What Vitamins Should I Be Taking, Doctor?

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A healthy 54-year-old, nonsmoking, omnivorous woman presenting for a routine examination asks about vitamin supplements. She expresses confusion about conflicting reports and recommendations. She currently uses no supplements.

THE CLINICAL PROBLEM

Medical teaching has been that, in generally healthy persons, nutritional needs can be readily met by diet alone. However, recent evidence shows that the use of folic acid supplements in early pregnancy can dramatically reduce the incidence of neural-tube defects; thus, at least in some circumstances, vitamin intake can be suboptimal without there being any clinical evidence of deficiency. Public interest in vitamin supplements is enormous, with 30 percent of the population of the United States currently using such supplements.[1] Political pressures have led to a highly unregulated industry with limited control by the Food and Drug Administration over marketing and quality.

STRATEGIES AND EVIDENCE

Ideally, vitamin supplements would be evaluated in randomized prevention trials with measurable clinical end points. However, such trials are complicated, and the results could be misleading. First, everyone has some level of consumption of vitamins, so the effect of a supplement depends on the amount of a given vitamin that is already being consumed. Because trial participants often have good diets, the results of a study finding no effect of a vitamin supplement might not apply to those with poorer diets. Moreover, a trial may be too short for an effect to be detected, particularly in the case of the incidence of cancer. In addition, to enhance their statistical power, many studies focus on persons at high risk for a disease or those with existing disease. If diet is not responsible for the elevated risk, such a focus could obscure a benefit that might be observable in a population with average risk. In general, clearly positive results would be compelling, but negative results would be difficult to interpret.

One approach is to discourage the use of vitamin supplements unless benefits are proved in randomized trials with measurable clinical outcomes. An alternative is to use all the available evidence to weigh the likelihood of a benefit against the likelihood of harm, while also considering the costs. Evidence should include the results of animal studies, randomized trials examining intermediate biologic markers, and observational epidemiologic studies with clinical end points. For example, a low intake of several micronutrients may cause DNA damage,[2] although the clinical effect of this damage is not known. Epidemiologic studies demonstrating a relation between low intake of a nutrient and the risk of disease suggest that at least part of the population has suboptimal intake.

Because foods contain many nutrients, distinguishing among the effects of various nutrients in the same foods can be difficult. For example, the observation that high-dose beta carotene supplementation in smokers did not reduce the risk of lung cancer and may even have increased risk[3] highlights the potential dangers of extrapolating from epidemiologic studies of food consumption (the consumption of fruits and vegetables, in this case) to concentrated forms of a single chemical. Epidemiologic studies of vitamin-supplement use per se are more directly relevant, but careful statistical adjustment for other lifestyle factors is essential because users of supplements may have healthier behavior in general than nonusers. We briefly review the potential effects of commonly used vitamins, recognizing that the relevant literature is far greater than what can be cited here.

Folic Acid

Several epidemiologic studies have found that periconceptional folic acid supplementation is associated with a substantially reduced risk of neural-tube defects (Fig. 1). In a randomized trial, a high-dose folic acid supplement reduced the incidence of recurrent neural-tube defects by 70 percent.[4] A randomized trial of a multivitamin that included folic acid (800 μg daily) in pregnant women without a history of an af-

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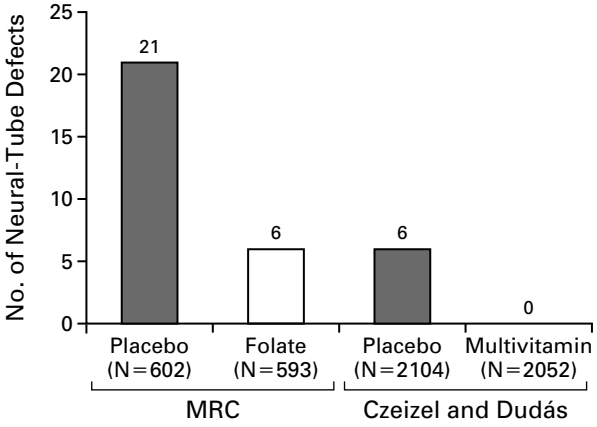

Figure 1. The Effect of Periconceptional Folic Acid Supplementation on the Incidence of Neural-Tube Defects.

Data are from studies by the Medical Research Council (MRC) Vitamin Study Research Group[4] and Czeizel and Dudás.[5]

fected pregnancy was stopped early because of a clear benefit.[5] This is the only definitively proven benefit of a multivitamin.

Although this relation has not been tested in randomized trials, substantial evidence suggests that low folic acid intake increases the risk of cardiovascular disease and several types of cancer. In many studies, high blood homocysteine levels have been associated with higher risks of coronary disease.[6] Inadequate intake of folic acid and, to a lesser extent, of vitamin B_6 and vitamin B_{12} increases homocysteine levels. Higher folic acid intake, the use of multivitamin supplements,[7] and higher blood folate levels[8] are all associated with a lower risk of coronary disease.

Higher intake of folic acid is associated with a lower risk of colon cancer[9] and breast cancer,[10,11] particularly among persons who are at increased risk because of daily alcohol consumption. Also, a polymorphism in the gene for methylenetetrahydrofolate reductase (which is involved in folate metabolism) has been associated with an increased risk of colon cancer in some studies,[12] providing additional evidence that the relation between low folic acid intake and an increased risk of colon cancer is causal. Alcohol interferes with folate absorption and metabolism, perhaps accounting for increased folate requirements among drinkers. When folate levels are low, uracil is inappropriately incorporated into DNA, and folic acid supplementation reverses this process.[13]

The optimal folic acid intake remains uncertain. An intake of 400 μg per day minimizes blood homocysteine levels in most people,[14] but more may be needed to reduce the risk of cancer. Although an intake of 400 μg of folate per day may be achieved by eating natural foods, the average American intake from these sources is about 200 μg per day. Since 1998, the food-fortification program in the United States has been adding about 100 μg per day. Thus, most people in this country still consume less than 400 μg per day, and users of multivitamins still have lower homocysteine levels than nonusers.[15]

Vitamin B_6

Vitamin B_6 intake below the U.S. recommended daily allowance (RDA) of 2 mg is associated with an increased risk of coronary disease, but it is unclear whether this association is independent of folic acid intake.[7] Meat and legumes are the major food sources of vitamin B_6; persons who reduce their consumption of red meat without increasing their consumption of legumes may have low vitamin B_6 intake.

Vitamin B_{12}

Low blood levels of vitamin B_{12} (serum cobalamin level, <258 pmol per liter), caused primarily by reduced absorption in elderly persons with low gastric acidity, are also associated with higher blood homocysteine levels.[14] Twelve percent of elderly persons may have inadequate vitamin B_{12} stores.[16] The consequences of marginal vitamin B_{12} status remain unclear, but they may include increased risks of vascular disease[17] and cancer.[18] Crystalline vitamin B_{12}, the form that is used in supplements, does not require gastric acid for absorption, so a multivitamin can ensure that intake is adequate for most people.

Vitamin D

Sun exposure alone can provide adequate vitamin D, but in the northern United States, ultraviolet radiation during the winter is insufficient to minimize the risk of osteoporosis and fractures.[19] Among patients admitted to a Boston hospital, 57 percent were deficient in vitamin D.[20] Few foods naturally contain vitamin D, and fortified milk is the primary dietary source. In a Finnish trial, an annual injection of vitamin D reduced the risk of fracture by 25 percent,[21] but no significant benefit was seen in a Dutch study.[22] The effect of supplementation depends on the amount of sun exposure a person receives and his or her dietary intake. However, reasonable evidence suggests that many Americans would benefit from supplemental vitamin D to reach the RDA of 400 IU, and double this amount may be desirable for some persons.[23] A vitamin D intake of up to 2000 IU per day is believed to be safe.

Vitamin A

Because vitamin A helps regulate cell differentiation, higher intakes could potentially reduce the risk of cancer. However, blood levels are tightly controlled, and greater intake in well-nourished persons has only a minimal effect on these levels. Both intake and blood

levels of vitamin A have generally been shown to be unrelated to the risk of cancer.[24] Supplemental beta carotene, a vitamin A precursor, has consistently failed to reduce the risk of cancer in randomized trials.

Intake of up to twice the RDA of vitamin A of 5000 IU is thought to be safe. However, an intake of preformed vitamin A (retinol) in the range of 10,000 IU per day or higher — which might be attainable from foods rich in vitamin A (especially liver, fortified breakfast cereals, and dairy products) in combination with a multivitamin containing the RDA of retinol — might be undesirable. Intakes of preformed vitamin A in this range have been associated with an increased risk of hip fracture,[25] and daily intakes of approximately 10,000 IU during pregnancy have been associated with specific birth defects,[26] but confirmation of these associations is needed.

Multivitamin Preparations

The most common supplements are multivitamins that typically include the RDA of thiamin, riboflavin, niacin, folic acid, and vitamins A, C, B_6, B_{12}, D, K, and E (Table 1). Few studies have evaluated the effects of multivitamins per se rather than specific components of them. In prospective studies, the daily use of a multivitamin has been associated with a lower risk of coronary disease,[7] colon cancer,[27,28] and breast cancer, particularly among regular consumers of alcohol.[10] In a randomized trial involving elderly persons, a multivitamin–multimineral combination reduced the number of days of illness due to infections by half.[29] A similar supplement reduced the incidence of stroke, primarily among men, in a nutritionally deficient population in China.[30] These results must be replicated in other settings.

Vitamin E Supplements

Vitamin E supplements, most of which contain 200 to 800 IU, lead to intakes far greater than the RDA of 30 IU and well beyond those attainable by diet. High doses of vitamin E block the oxidative modification of low-density lipoprotein cholesterol and have additional effects that might reduce the risk of coronary disease.[31] However, the value of vitamin E for the prevention of cardiovascular disease is controversial. In prospective, observational studies involving persons without known cardiovascular disease, the use of vitamin E supplements for two or more years — most commonly at a dose of 400 IU per day — has been associated with a 20 to 40 percent reduction in the risk of coronary disease.[32] The one negative prospective study included few users of the supplements, and information on the duration of use was not collected.[31]

The published randomized trials, in contrast to these observational studies, have focused primarily on persons with existing coronary disease, and their results are inconsistent. Although the incidence of recurrent infarction was reduced by half in one study,[33] supplementation with vitamin E (400 IU daily) had no effect on cardiovascular events in the substantially larger Heart Outcomes Prevention Evaluation trial.[34] The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico found no significant differences in the overall cardiovascular end points, but there was a significant reduction in the rate of death due to cardiac causes.[35] One recent trial showed a significant halving of the rate of cardiovascular outcomes among patients on dialysis,[36] and another demonstrated a large reduction in the rate of progression of intima–media thickness among men (but not women) randomly assigned to receive a combination of vitamin E and vitamin C.[37] No effect of vitamin E was seen among high-risk patients in a recent trial, but the intervention ended at 3.6 years.[38]

Thus, the weight of evidence is against an important short-term benefit of vitamin E supplements among patients with existing cardiovascular disease who are being treated with multiple pharmacologic agents. The long-term benefits of vitamin E supplementation for primary prevention remain unclear.

It has also been hypothesized that vitamin E supplements reduce the risk of cancer. No benefit has been found in terms of the risk of breast cancer,[39] and data on the risk of colon cancer are mixed.[40,41] The randomized Alpha-Tocopherol Beta Carotene Cancer Prevention Study found an unexpected, significant reduction in the incidence of prostate cancer[42] but not in the incidence of other types of cancer. Be-

Table 1. Nutrient Content of a Multivitamin Supplement Supplying the Recommended Daily Allowance of Its Components.*

Vitamin	Amount per Pill
Vitamin A†	5000 IU
Vitamin C	60 mg
Vitamin D	400 IU
Vitamin E	30 IU
Thiamin (B_1)	1.5 mg
Riboflavin (B_2)	1.7 mg
Niacin	20 mg
Vitamin B_6	2 mg
Folic acid	400 μg
Vitamin B_{12}	6 μg
Pantothenic acid	10 mg

*The amount of each vitamin contained in each pill provides 100 percent of the U.S. recommended daily allowance for that vitamin.

†Twenty percent of the activity of vitamin A is derived from beta carotene.

cause many cancer sites were examined, this may represent a chance finding.[43] Sparse evidence suggests that vitamin E may slow the progression of Alzheimer's disease.[44]

Vitamin E intake of up to at least 1000 IU per day is generally considered safe.[45] A nonsignificant increase in the incidence of hemorrhagic stroke was seen in the Alpha-Tocopherol Beta Carotene trial, which included only men who smoked,[42] but such an increase was not observed in a cohort composed primarily of nonsmokers.[46] Vitamin E supplementation may accelerate the progression of disease in patients with retinitis pigmentosa.[47]

Vitamin C Supplements

Little evidence supports the existence of a benefit of vitamin C supplementation beyond the range of the typical diet in the United States or the current RDA of 90 mg for men and 75 mg for women (35 mg higher for smokers), and minimal effects might be expected from supplementation because tissues become saturated at about these levels of intake.[45] Vitamin C supplements have been associated with a lower risk of coronary disease in one cohort study,[48] but the analysis did not control for the use of vitamin E supplements.

Many studies have found an association between a low dietary intake of vitamin C and an increased risk of stomach cancer,[24] but the effects of vitamin C supplements have not been specifically evaluated. Even long-term supplementation with vitamin C was not associated with a lower risk of breast cancer.[39] Fewer data are available on associations with other types of cancer, but there is no compelling evidence of a benefit.[45]

AREAS OF UNCERTAINTY

Few of the many possible associations between specific vitamins and specific diseases have been examined in randomized clinical trials. The evidence that folic acid reduces the risk of coronary disease and of colon cancer is strong, although not definitive. Even in instances in which a benefit has been proved, as in the case of the reduction in the incidence of neural-tube defects by folic acid supplementation, the optimal dose is uncertain. Requirements for nutrients may be influenced by genetic variations, and this is a focus of ongoing research.

GUIDELINES

Guidelines from some professional societies or governmental panels recommend attempting to obtain vitamins and minerals from food sources rather than from supplements.[49,50] The American Dietetic Association and the U.S. Dietary Guidelines also note that some people may need vitamin or mineral supplements in addition to a good diet to ensure that their nutritional needs are met.[51,52] The U.S. Preventive Services Task Force emphasizes the need for folic acid supplements for women planning a pregnancy,[53] and the Centers for Disease Control and Prevention recommend supplemental folic acid for premenopausal women who could potentially become pregnant. The Food and Nutrition Board of the Institute of Medicine notes that there has been no resolution of the question regarding the effect of antioxidant vitamins on the risk of chronic disease.[45]

CONCLUSIONS AND RECOMMENDATIONS

Given the greater likelihood of benefit than harm, and considering the low cost, we conclude that a daily multivitamin that does not exceed the RDA of its component vitamins makes sense for most adults, including the woman in the case vignette. Substantial data suggest that higher intakes of folic acid, vitamin B_6, vitamin B_{12}, and vitamin D will benefit many people, and a multivitamin will ensure an adequate intake of other vitamins for which the evidence of benefit is indirect.[54] A multivitamin is especially important for women who might become pregnant; for persons who regularly consume one or two alcoholic drinks per day; for the elderly, who tend to absorb vitamin B_{12} poorly and are often deficient in vitamin D; for vegans, who require supplemental vitamin B_{12}; and for poor urban residents, who may be unable to afford adequate intakes of fruit and vegetables.

Many multivitamins also include essential minerals, although the doses of some of these minerals, such as calcium, are well below the RDA. Although we have not discussed minerals here, there is less evidence supporting the existence of a benefit for mineral supplements, with the exception of the additional iron required by some premenopausal women.

Although one could measure blood levels to identify those who would benefit most from multivitamins, this would be much more expensive than simply recommending that all adults take a supplement (at a typical cost of $20 to $40 per year). Education regarding nutrition is vitally important, but it has been far less effective than supplementation or the fortification of food in raising blood folic acid levels.[55,56] However, a vitamin pill is no substitute for a healthful lifestyle or diet, because foods contain additional important components, such as fiber and essential fatty acids. In particular, a vitamin supplement cannot begin to compensate for the massive risks associated with smoking, obesity, or inactivity. The cost of a multivitamin supplement is so low — similar to that of about a quarter of a serving of fruit or vegetables — that it is unlikely to displace healthful foods in most persons' budgets.

We also believe that vitamin E supplements are reasonable for most middle-aged and older Americans who are at increased risk for coronary disease. Evidence is still accruing, but even assuming a low probability that vitamin E will eventually be proved efficacious (and we view the probability as fairly high),

the likelihood of a benefit would still outweigh the very low probability of harm. We would offer a vitamin E supplement in a dose of 400 IU as an option to the patient in the case vignette, with the suggestion that we review this practice annually as more information becomes available. Finally, although we do not recommend additional vitamin supplements at present, the relevant evidence remains far from complete.

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