**To Our Readers**

The current issue of the Updates Series on Nutrition in Disease Management features two articles. The first of these addresses an issue which is very relevant to every practitioner of Clinical Medicine - ‘Rational Use of Vitamin Supplements In Clinical Practice: The Evidence For And Against’.

The second article on 'The Role of Enteral Nutrition in Chronic Medical Disorders' highlights the issues to be considered in designing on enteral nutrition supplement and also draws attention to the need to urgently set Recommended Dietary Intakes (RDIs) for micronutrients which are applicable in the Indian context.

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**Rational Use Of Vitamin Supplements in Clinical Practice: The Evidence For And Against**

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It is not unusual for a clinician to face the dilemma of whether to prescribe a vitamin supplement or not. The classical teaching is that in healthy patients on a normal diet, all the nutrient needs of the individual are met by the diet. Of late, doctors are prescribing vitamin supplements frequently and a large number of individuals are consuming them. In the US, 30 per cent of the population is using such supplements.1

**LIMITATIONS OF STUDIES ON VITAMINS**

The ideal method to evaluate the need for vitamin supplementation would be a randomised controlled trial with measurable clinical end points. Unfortunately, these trials are clinically not possible due to the following reasons:

- The food that a person eats already contains some amount of vitamins. Thus the effect of a supplement is confounded by the already existing intake of the vitamin.
- The subjects included in these trials are from the general population, so they may not have pre-existing vitamin deficiencies and therefore, there may be no significant effect of Vitamin supplemental demonstrable in such a setting.
- The trials may require to be subjected to a long-term follow-up before an effect of vitamin supplementation can be detected.

A limitation of epidemiological studies using different foodstuffs is that a single foodstuff contains more than one nutrient. As a result, the effect observed could be attributable to other nutrients in the study foodstuff. 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 risk2 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. This review discusses the evidence available for use of vitamin supplementation including the results of animal studies, randomized trials examining intermediate biologic markers, and observational epidemiological studies with clinical end points.

**Folic Acid**

There is substantial evidence through epidemiologic studies that periconceptional folic acid supplementation is associated with a substantially reduced risk of neural-tube defects. In a randomized trial, a high-dose folic acid supplement reduced the incidence of recurrent neural-tube defects by 70 percent.3 A randomized trial of a multivitamin that included folic acid (800 µg daily) in pregnant women without a history of an affected pregnancy was stopped early because of a clear benefit.4 This is the only definitively proven benefit of a multivitamin.

Inadequate intake of folic acid and, to a lesser extent, of vitamin B6 and vitamin B12 contributes to increased homocysteine levels, which is associated with an increased risk of coronary artery disease.5 Evidence exists that low folic acid intake increases risk of cardiovascular disease and several types of cancer. High intake of folic acid, the use of multivitamin supplements,6 and higher blood folate levels7 are all associated with a lower risk of coronary disease.

Folate absorption and metabolism is influenced by alcohol thus leading to increased folic acid requirement in alcoholics. When folate levels are low, uracil is inappropriately incorporated into DNA, and folic acid supplementation reverses this process.12 Higher intake of folic acid is associated with a lower risk of colon cancer8 and breast cancer,9,10 especially among persons who are at increased risk because of daily alcohol consumption. Additional evidence for the casual relationship between low folic acid intake and an increased risk of colon cancer is obtained from the fact that 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.11 The optimal folic acid intake remains uncertain. An intake of 400 µg per day minimises blood homocysteine levels in most individuals,13 but a higher dose may be required to reduce the risk of cancer. The daily intake of folic acid in an Indian has not been determined, but in America it is not more than 200µg per day, thereby justifying the start of food fortification programme since 1998 in the USA. Users of multivitamins in USA have lower homocysteine levels than nonusers.14

**Vitamin B6 :** Vitamin B6 intake below the recommended daily allowance (RDA) of 2 mg is associated with an increased risk of coronary disease, but whether this effect is independent of folic acid intake is not clear.6

**Vitamin B12 :** High blood homocysteine levels are seen in patients with low blood 3 levels of vitamin B12 (serum cobalamin level, <258 pmol per liter). In the elderly this may be primarily due to reduced
absorption resulting from low gastric acidity. The consequences of marginal vitamin B12 status remain unclear, but they may include increased risk of vascular disease and cancer. Crystalline vitamin B12 (the form that is used in supplements) does not require gastric acid for absorption, so a multivitamin preparation can ensure that intake is adequate for most people. In the Indian population B12 deficiency may be because of lower dietary intake owing to a largely vegetarian diet and malabsorption.

**Vitamin D**: Adequate exposure to the sun is sufficient to provide the daily requirement of vitamin D. In hospitalised patients vitamin D deficiency may be seen in up to 57 per cent of patients. Few foods naturally contain vitamin D and fortified milk is the primary dietary source. An annual injection of vitamin D has been shown to reduce the risk of fracture by 25 percent, but no significant benefit was seen in a Dutch study. The effect of supplementation depends on the amount of sun exposure a person receives and his or her dietary intake. A vitamin D intake of up to 2000 IU per day is believed to be safe.

There is evidence 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.

**Vitamin A**: Theoretically vitamin A helps regulate cell differentiation and it could potentially reduce the risk of cancer. But, both intake and blood levels of vitamin A have not been shown to be related to the risk of cancer. Supplemental beta carotene, a vitamin A precursor, has consistently failed to reduce the risk of cancer in randomized trials.

An intake of preformed vitamin A (retinol) in the range of 10,000 IU per day or higher – has been associated with an increased risk of hip fracture and daily intakes of approximately 10,000 IU during pregnancy has been associated with specific birth defects, 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, B6, B12, D, K, and E. 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, colon cancer, and breast cancer. This is more so for patients consuming alcohol. In elderly persons, a multivitamin–multimineral combination reduced the number of days of illness due to infections by half. Another study from China showed reduced incidence of stroke, primarily among men, in a nutritionally deficient population. More studies need to be done to corroborate these results.

**Vitamin E Supplements**: The RDA of vitamin E is 30 IU. Vitamin E supplements contain 200 to 600 IU which cannot be achieved 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. 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.

The results of randomised trials are inconsistent and these studies have used patients with existing coronary disease. One small study showed a decreased incidence of recurrent infarction. In the Heart Outcomes Prevention Evaluation trial supplementation with vitamin E (400 IU daily) had no effect on cardiovascular events. The GISSI trial found no significant differences in the overall cardiovascular endpoints, but the reduction in death rates from cardiac causes was significant. Two recent trials using a combination of vitamin E and vitamin C showed a significant positive role of these vitamins in coronary artery disease. No effect of vitamin E was seen among high-risk patients in a recent trial. In this trial the patients were only followed up for a mean of three and a half years.
Thus, the weight of evidence does not favor an important short-term benefit of vitamin E supplements among patients with existing cardiovascular disease who are being treated with multiple pharmacologic agents. It seems that vitamin E supplementation for primary prevention may have a role but this is a subject of further study.

There has been an interest in vitamin E as an agent to prevent cancer. No benefit has been found in terms of the risk of breast cancer,36 and data on the risk of colon cancer are mixed.37,38 The randomized Alpha-Tocopherol Beta Carotene Cancer Prevention Study found an unexpected, significant reduction in the incidence of prostate cancer39 but not in the incidence of other types of cancer. This may just be a chance finding as multiple cancer sites were examined in this study. The role of vitamin E in slowing the progression of Alzheimer’s disease needs further evaluation. 40

How safe is supplementation of vitamin E? Vitamin E intake of up to 1000 IU per day is generally considered safe.41 An increase in the incidence of hemorrhagic stroke was seen in the Alpha-Tocopherol Beta Carotene trial, which included only men who smoked,39 but such an increase was not observed in a cohort composed primarily of nonsmokers.42 Patients with retinitis pigmentosa may have an acceleration in the progression of the disease.43

**Vitamin C Supplements:** There is not much evidence to support vitamin C supplementation over and above the daily requirement. Vitamin C supplements have been associated with a lower risk of coronary disease in one cohort study,44 but the analysis did not control for the use of vitamin E supplements.

There are studies showing an association between a low dietary intake of vitamin C and an increased risk of stomach cancer,21 but the effects of vitamin C supplements have not been specifically evaluated. Long-term Vitamin C supplementation has not lead to a lower risk of breast cancer.36 There is no compelling evidence of a benefit in other cancers too.41

**AREAS OF UNCERTAINTY**

It is easy to describe the studies conducted, but a difficult task to put forth practical guidelines. There are very few randomised controlled trials. There can be multiple confounding factors, especially genetic variations and other nutrients such as folic acid, vitamin B6, vitamin B12, and vitamin D could exert a beneficial effect. Multivitamin supplementation should ensure an adequate intake of other vitamins for which the evidence of benefit is indirect.54 The population groups that may particularly benefit include pregnant women, persons who regularly consume one or two alcoholic drinks per day; elderly people, who are deficient in dietary intake and tend to absorb vitamin B12 poorly and are often deficient in vitamin D; vegetarians, who require supplemental vitamin B12; and finally poor urban residents, who may be unable to afford adequate intakes of fruit and vegetables. Regarding vitamin E, supplementation is reasonable for most middle-aged and older people who are at increased risk for coronary disease. Evidence is still coming, but even assuming a low probability that vitamin E will eventually be proved efficacious, the likelihood of a benefit would still outweigh the very low probability of harm.

Last but not the least, a vitamin pill is no substitute for a healthy 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.
REFERENCES


IX ANNUAL CONFERENCE OF PENSA

The IX Annual Conference of PENSA (Parenteral and Enteral Nutrition Society of Asia) will be held from November 6-8, 2003 at Goa, India and will be organised by the ISPEN Maharashtra Chapter. India is hosting the PENSA Meeting for the first time.
1. In children with cystic fibrosis, parenteral nutrition has been shown to correct a deficiency of
   - a. Oleic acid.
   - b. Linoleic acid
   - c. Palmitic acid
   - d. Linolenic acid

2. Which of the following would most likely need to be withheld from the parenteral nutrition of infants with cholestatic liver disease?
   - a. Chromium and copper
   - b. Copper and manganese
   - c. Selenium and chromium
   - d. Manganese and selenium

3. Which of the following best characterizes how patients and their families view home parenteral nutrition?
   - a. Source of self-esteem
   - b. Overwhelming burden
   - c. Life-sustaining therapy
   - d. Source of embarrassment

4. In infants and children receiving parenteral nutrition, it may be difficult to administer adequate amounts of
   - a. Copper.
   - b. Calcium
   - c. Vitamin E
   - d. Magnesium

5. Which of the following is recommended for an infant with hyperbilirubinemia receiving parenteral nutrition?
   - a. Increase daily amino acids to 4g/kg
   - b. Limit dextrose concentration to 10%
   - c. Limit intravenous fat emulsions to 2-4% of kilocalories
   - d. Use peripheral rather than central parenteral nutrition

6. In which of the following should patients receiving home parenteral nutrition and their caregivers be trained
   - a. use a 0.22µm filter on the intravenous tubing
   - b. store home parenteral nutrition at room temperature
   - c. inspect for infusate contamination, precipitate, or inhomogeneity
   - d. recognize and report symptoms of essential fatty acid deficiency

7. Which of the following is an advantage of using a peripheral vein rather than an umbilical artery catheter to deliver parenteral nutrition solution in neonates?
   - a. Decreased risk of kidney damage
- b. Fewer site changes from infiltrations
- c. Lower glucose concentration
- d. Less skin sloughing

8. Which of the following best characterizes the usual difference in nutritional requirements of a full-term infant receiving extracorporeal life support and parenteral nutrition compared to a similar infant receiving parenteral nutrition alone?

- a. Increased fluid
- b. Increased protein
- c. Increased sodium
- d. Decreased sodium

9. In a penicillin allergic patient with Crohn’s disease receiving home parenteral nutrition and scheduled for extensive oral surgery, which of the following is recommended for oral prophylaxis against bacterial endocarditis?

- a. Ampicillin
- b. Amoxicillin
- c. Clindamycin
- d. Vancomycin

10. Which of the following best describes parenteral nutrition-related bone disease in preterm infants

- a. Bone mineralization is enhanced by diuretics such as furosemide
- b. Alternating calcium and phosphorus each day in the parenteral nutrition will maximize mineral delivery
- c. Methods of prevention include provision of 2-3 times the normal amount of vitamin D
- d. It is associated with increased serum alkaline phosphatase and urinary calcium, and decreased urinary phosphorus
1 (b) Children with cystic fibrosis are often deficient in fatty acids. Linoleic acid deficiency has been documented in patients with cystic fibrosis and nutritional impairment. Correction of linoleic acid deficiency can be achieved by parenteral administration of fat emulsions.

2 (b) Both manganese and copper are excreted through bile and may need to be withheld from parenteral nutrition in cholestatic liver disease. Since chromium and selenium are excreted mainly in the urine, dose adjustments of these trace elements may be required in renal failure.

3 (c) Despite many problems associated with the use of home parenteral nutrition, in a recent study of patients, the technology was highly valued as life-sustaining as therapy.

4 (b) Due to the insolubility of calcium phosphate, it may be difficult to provide adequate amounts of calcium and phosphorus for infants and children in parenteral solutions. Adequate doses of magnesium, vitamin E, and copper can easily be provided.

5 (c) Since free fatty acids displace bound bilirubin from albumin, thereby increasing the risk of kernicterus, it is recommended that intravenous fat emulsions be restricted in infants with hyperbilirubinemia receiving parenteral nutrition. Lipid should be provided in an amount to prevent essential fatty acid deficiency (2-4% of kilocalories). The amount of amino acids and dextrose, as well as the route of administration, do not affect the risk of kernicterus in these infants.

6 (c) According to A.S.P.E.N. Standards for Home Nutrition Support, the patient/caregiver should receive education regarding the inspection of home parenteral nutrition solutions. Competence in the recognition of solution contamination, precipitate, or inhomogeneity should be demonstrated to prevent associated complications.

7 (a) A glucose concentration of 10-12% is the highest amount tolerated in peripheral veins in a neonate and this limits the amount of kilocalories that can be provided. Infiltration of intravenous fluids is a frequent problem with peripheral vein delivery, which requires a great deal of nursing time for restarting the lines. If an umbilical artery catheter is misplaced, infusion of a hypertonic solution into the renal artery can cause kidney damage.

8 (d) Infants placed on extracorporeal life support often are fluid overloaded due to resuscitation and have received sodium from sources such as sodium bicarbonate, normal saline, and albumin. Therefore, most infants on such support are sodium and fluid restricted. Unless a patient develops renal failure, the normal protein load for age is provided.

9 (c) Amoxicillin and ampicillin should not be used for prophylaxis in patients who are allergic to penicillin. Vancomycin is not systemically absorbed from the gastrointestinal tract and is only given orally for pseudomembranous colitis. The American Heart Association recommends clindamycin 300 mg orally 1 hour before procedure and 150 mg 6 hours after initial dose for penicillin-allergic patients.

10 (d) In premature infants, parenteral nutrition related bone disease is associated with increased serum alkaline phosphatase and urinary calcium, and decreased urinary phosphorus. Better calcium and phosphorus retention rates in preterm infants are achieved when calcium and phosphorus are infused together. Parenteral vitamin D requirements have not been shown to exceed normal needs. Excessive parenteral vitamin D may increase urinary mineral excretion. Chronic use of diuretics, such as furosemide, may enhance urinary mineral excretion not bone mineralization.