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Folic acid can reduce suffering and save lives

Editorial:

Folate (the term generally used for the naturally occurring form of this B vitamin in foods) has a vital role in health maintenance. It is involved in the synthesis of nucleic acids, the molecules that carry the genetic information in cells, and is particularly important for the proper formation of nerves and blood cells. Many metabolic reactions necessary for normal growth and body functions also depend on an adequate supply of folate. The richest food sources of folate are liver, dark green leafy vegetables, beans, yeast and orange juice. In some countries, cereal products (e.g. flour, bread, breakfast cereals) are fortified with folic acid.

Folate deficiency is nevertheless widely encountered, even in European countries. In a recent nutritional survey conducted in Germany, for example,

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median dietary intake of folate was less than 0.3 mg daily. Only about 10% of the population surveyed achieved the recommended intake from food (see *Beitz et al. in this issue*). A poor folate status may still occur in spite of apparently adequate intakes. Considerable amounts of folate are lost during food storage and preparation, and uptake from the intestines is poor and erratic (less than half of the natural folate in food reaches the blood stream). Another reason that has received considerable attention recently is the existence, in 10–45% of the population, of a genetic mutation of an enzyme (methylenetetrahydrofolate reductase: MTHFR) that increases folic acid requirements.

The clinical manifestation of severe folate deficiency, megaloblastic anaemia, is relatively rare these days. It is usually restricted to people with absorption disorders, such as frail elderly patients and alcoholics. Because of their restricted diets, these people also experience deficiencies of other vitamins (in particular vitamin B12). What currently concerns public health authorities more, however, are the effects of marginal folate deficiency on pregnancy outcomes, cardiovascular health, and cancer incidence.

Pregnant women need more folate than nonpregnant women, because of the high demands made by the rapidly growing foetus. Poor folate status in pregnancy increases the risk for abortion, premature delivery, low birth weight, and birth defects. One of the most devastating effects of folate deficiency on the unborn infant is malformation of the brain and spine. These “neural tube defects” (NTD) develop in the early stages of pregnancy. If the baby survives, it is likely to suffer extensive paralysis, and may be physically and mentally handicapped for the rest of its life. Research has shown that most women can reduce the risk of NTD by 50–70% if they take a supplement containing at least 0.4 mg folic acid every day. It is important that they begin taking it before they become pregnant, and continue for at least 2 months after conception.

Diseases of the heart and blood vessels (heart attack, stroke, embolism) cause more deaths and ill health in Europeans than any other disorder. Numerous factors have been identified that increase the risk. These include overweight, high blood pressure, high blood cholesterol, smoking, diabetes and lack of exercise. Recently, scientists have found another, independent, risk factor: high blood levels of a molecule called “homocysteine”. This is an intermediate in the synthesis of cysteine and in the recycling of methionine. The latter process involves enzymes that depend on an adequate supply of micronutrients, in particular folic acid and vitamin B12. If the enzymes do not work efficiently, too much homocysteine stays in the blood. Fortunately, high homocysteine levels can be corrected by taking a supplement containing folic acid or even better folic acid plus vitamin B12. It has now been confirmed that high homocysteine levels do cause cardiovascular disease, and that the risk can be reduced by increasing intakes of folic acid (see *Wald et al. in this issue*).

The development of cancer, another major cause of premature death, has also been linked to folate deficiency. Abnormal cells from which cancers can develop are more commonly found in people with a poor folate status. In a recent study on patients at high risk for colon cancer, folate supplementation reduced the activity of abnormal cells in the rectum (see *Khosraviani et al. in this issue*). The strongest evidence for a protective effect of folic acid supplementation against cancer comes from studies on patients with ulcerative

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colitis (a chronic disease of the large bowel often complicated by colorectal cancer). Cancer development in those patients who took folic acid was significantly lower than in those who did not.

Pregnancy complications, cardiovascular diseases and cancer put a considerable strain on healthcare budgets, as well as causing widespread suffering. Surely this is unacceptable when they can be controlled simply and cost-effectively with folic acid supplementation (*see Postma et al. in this issue, and Tice et al. in 4/2001*).

A. Bowley, Editor

PREVENTION OF CARDIOVASCULAR DISEASE

High homocysteine is a cause of cardiovascular disease

Review

To assess the relationship between serum homocysteine concentrations and the risk for ischaemic heart disease, deep vein thrombosis with or without pulmonary embolism, and stroke, Wald et al. analysed available relevant studies. This included 72 studies on the prevalence of the genetic variant of the MTHFR enzyme (in 16,849 cases), and 20 prospective studies (with 3,820 participants) on homocysteine concentration and disease risk.

Both types of study show a significant association between homocysteine and risk. Individuals with the MTHFR variant had a 1.42 higher odds ratio for heart disease, a 1.6 higher odds ratio for thrombosis/embolism, and a 1.65 higher odds ratio for stroke (for a 5-micromol/l increase in serum homocysteine). In the prospective studies, odds ratios for an increase of 5 micromol/l homocysteine were 1.32 (for heart disease) and 1.59 (for stroke). There were no prospective studies on thrombosis/embolism.

Conclusion

These results strengthen the evidence that a raised serum homocysteine concentration is a cause of cardiovascular disease. Lowering serum homocysteine by 3 micromol/l (by taking a daily supplement containing 0.8 mg folic acid) should reduce the risk of ischaemic heart disease by 16%, deep vein thrombosis by 25%, and stroke by 24%.

Source

Wald DS, Law M, Morris JK. Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. *Brit Med J* 2002; 325: 1202–1207.

Vitamin E in CVD: A look at the evidence

Review

A great deal of evidence shows that the risk for cardiovascular disease (CVD) can be reduced by protecting low density lipoproteins (LDL) against

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oxidation. Clinical trials designed to confirm this hypothesis have, however, produced conflicting results. Blumberg summarises currently available results, and investigates why we still do not know if vitamin E can prevent CVD.

Observational studies on primary prevention strongly suggest that vitamin E slows the formation of atherosclerotic plaque, which already begins in childhood. Studies on secondary prevention (i.e. in people already affected by CVD symptoms) might therefore begin too late. He criticises that all the large clinical trials done so far have failed to test the capacity of vitamin E to reduce oxidative stress. He notes that higher doses and longer periods of treatment than those used might be needed to achieve a measurable effect. It is also important, considering possible nutrient interactions, to examine whether an antioxidant cocktail would be more effective than vitamin E alone.

Conclusion

Use of vitamin E supplements is not without a rational basis. Overall evidence from basic and clinical research is positive, and justifies further investigations. Vitamin E supplementation not only reduces the susceptibility of LDL to oxidation, it also provides benefits in several other chronic diseases associated with oxidative stress.

Source

Blumberg JB. An update: Vitamin E supplementation and heart disease. Nutr Gen Care 2002; 5: 50–55.

Vitamin E fails to stop progression of atherosclerosis

Intervention

The VEAPS Research Group treated 258 men and women at low risk for CVD for three years with vitamin E (400 IU daily) or placebo, and measured the rate of change in thickness of the carotid artery intima-media (the inner and middle layers of the main neck artery). Intima-media thickness (IMT) is an indicator of atherosclerosis progression.

Vitamin E significantly reduced circulating levels of oxidised low density lipoproteins (LDL) and LDL oxidising capacity, but did not influence IMT progression.

Conclusion

Vitamin E supplementation had no perceptible effect on atherosclerosis progression in these well-nourished, healthy individuals at low risk for CVD. These results are consistent with earlier clinical trials. The data do not exclude the possibility of an effect in other populations (*see Iannuzzi et al. below, and Salonen et al. in 1/2001*).

Source

Hodis HN, Mack WJ, LaBree L, et al. Alpha-tocopherol supplementation in healthy individuals reduces low-density lipoprotein oxidation but not atherosclerosis. The Vitamin E Atherosclerosis Prevention Study (VEAPS). Circulation 2002; 106: 1453–1459.

Poor vitamin E status favours atherosclerosis

Intervention

Iannuzzi et al. examined 307 healthy middle-aged women (participants in a population-based study on the etiology of CVD and cancer) by ultrasound to detect early signs of carotid atherosclerosis. They also measured plasma concentrations of vitamin A, vitamin E and carotenoids, and evaluated dietary intakes with a food–frequency questionnaire.

The presence of atherosclerotic plaques at the carotid bifurcation (where atherosclerosis usually begins) was inversely related to vitamin E intake, as well as to the ratio of plasma vitamin E to plasma cholesterol. Only women in the highest tertile of vitamin E intake consumed more than 8 mg daily (current recommendations for women are between 12 and 15 mg). There was no association between the presence of carotid plaques and the other antioxidant nutrients measured.

Conclusion

This result supports the hypothesis that low vitamin E intake increases the risk for atherosclerosis.

Source

Iannuzzi A, Celentano E, Panico S, et al. Dietary and circulating antioxidant vitamins in relation to carotid plaques in middle-aged women. Am J Clin Nutr 2002; 76: 582–587.

NUTRITION IN PREGNANCY AND LACTATION

Periconceptional folic acid has economic benefits

Analysis

To estimate cost-effectiveness of periconceptional supplementation with folic acid, Postma et al. measured direct lifetime costs of care for patients born with an open spine (cost of medical care, special education and living arrangements) and weighed them against the cost of supplementation and expected benefits (longer life expectancy).

Lifetime costs of care in the Netherlands range between €70,000 and €114,000 per case; the cost of folic acid supplementation is about €25–35 per live birth. A gain in 10 life-years per case prevented was assumed. A conservative estimate of cost-effectiveness (based on a 50% effectiveness, supplementation costs of €30 per live birth, and lifetime cost of care at €90,000) resulted in net costs of €1800, which the authors consider to be very favourable.

Conclusion

Folic acid supplementation before pregnancy is economically justified. Greater efforts should be made to encourage it. This can be done through targeted education by healthcare workers, such as pharmacists.

Source

Postma MJ, Londeman J, Veenstra M, et al. Cost-effectiveness of periconceptional supplementation of folic acid. Pharm World Sci 2002; 24: 8–11.

PREVENTION OF CANCER

Folate reduces abnormal cell activity in rectal crypts**Intervention**

Animal studies have shown that changes in mucosal crypt cells of the colon induced nutritionally are directly related to changes in cancer risk. To determine the effect of folate supplementation (2 mg daily for 12 weeks) on colorectal cancer risk, Khosraviani et al. measured proliferation (multiplication) of rectal mucosa cells in 11 patients with recurrent rectal polyps (a group at high risk for colorectal cancer). This was achieved by counting the total number of cells and the actively growing cells in crypts (microscopically small folds in the rectal surface) in biopsies taken before treatment and after 4, 12 and 18 weeks, and calculating an index of cell activity.

In the patients given folate supplementation, the cell index fell from 9.1 to 7.4 after 12 weeks, while that of the control group did not change. The reduction in cell proliferation was mainly at the upper end of the crypts, where it is thought to reflect defective control of cell proliferation.

Conclusion

These data indicate that folate supplementation decreases proliferation of mucosal cells in the colon of patients at high risk for colon cancer.

Source

Khosraviani K, Weir HP, Hamilton P, et al. Effect of folate supplementation on mucosal cell proliferation in high risk patients for colon cancer. Gut 2002; 51: 195–199.

Selenium supplements can protect men against cancer**Intervention**

Duffield-Lillico et al. analysed additional data from the Nutritional Prevention of Cancer Trial, which was originally designed to test the efficacy of selenium supplementation (200 µg daily) in preventing nonmelanoma skin cancer recurrence. The report includes data collected between January 1st 1994 and February 1st 1996 (extending mean subject follow-up time by one year to an average of 7.4 years), and reviews effects on all cancers.

At the end of the study, total cancer incidence in the supplemented group was a significant 25% lower than in the placebo group (49% lower in participants with low baseline selenium levels). The protective effect was strongest on prostate cancer (–48%) and colorectal cancer (–54%).

Conclusion

These data continue to provide support for the efficacy of selenium supplementation in reducing cancer incidence and mortality. The protective effect on total cancer incidence was most prominent in males with low baseline selenium levels.

Source

Duffield-Lillico AJ, Reis ME, Turnbull BW, et al. Baseline characteristics and the effect of selenium supplementation on cancer incidence in a randomized

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clinical trial: A summary report of the Nutritional Prevention of Cancer Trial. Cancer Epidemiol Biomark Prev 2002; 11: 630–639.

Antioxidant supplements without effect on colorectal cancer risk in smokers

Intervention

In a follow-up to the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study (which tested the effects of daily supplementation with 50 mg vitamin E, 20 mg beta-carotene or both on cancer incidence), Malila et al. calculated the relative risks for colorectal cancer in 29,951 middle-aged, male smokers. At the time of analysis, 184 cases of colorectal cancer had been diagnosed (over an eight-year period).

The authors found no significant associations between dietary intake or blood levels of antioxidant micronutrients (including carotenoids) and colorectal cancer risk.

Conclusion

These data support the results of earlier studies.

Source

Malila N, Virtamo J, Virtanen M, et al. Dietary and serum α -tocopherol, β -carotene and retinol, and risk for colorectal cancer in male smokers. Eur J Clin Nutr 2002; 56: 615–621.

NUTRITION AND BONE HEALTH

Vitamin D insufficiency in elderly needs attention

Survey

To assess the prevalence of vitamin D insufficiency in patients attending a falls clinic in Southeast London, Dhesi et al. investigated the medical and social history of 400 consecutive patients, and measured their serum levels of vitamin D, calcium, phosphate, alkaline phosphatase and albumin.

Among the 374 patients with a complete analysis, 31.8% were severely deficient (serum vitamin D less than 12 $\mu\text{g/l}$) and 40.6% were moderately deficient (12–20 $\mu\text{g/l}$). Only 1.3% had adequate vitamin D levels (above 40 $\mu\text{g/l}$). It was difficult to predict the individual risk on the basis of the patient's history.

Conclusion

The prevalence of vitamin D insufficiency in these patients is very high. Because the benefits of vitamin D supplementation for older people are clear, it might be preferable to supplement all falls-clinic attendees.

Source

Dhesi JK, Moniz C, Close JCT, et al. A rationale for vitamin D prescribing in a falls clinic population. Age & Ageing 2002; 31: 267–271.

Many Germans have low dietary vitamin intakes

Survey

To analyse Germans' vitamin intakes, including the contribution by dietary supplements, Beitz et al. conducted interviews with 4030 adults participating in the 1998 German National Health Interview and Examination Survey.

A considerable percentage of the study population did not achieve the recommended intakes for several vitamins. Among men who did not regularly take supplements, about 90% had low folate intakes, two-thirds had low vitamin E intakes, and almost one-third had low vitamin C intakes. Among women, 97% had low folate intakes, more than two-thirds had low vitamin E intakes, and about one-third had low intakes of vitamins C, B1 and B2. Supplements were taken regularly by 38% of men and 48% of women. Even with these supplements, 39% of the men and 28% of the women still had intakes of folate below the reference value, while 17% and 11% respectively still had low intakes of vitamin E.

Conclusion

A substantial part of the German population takes supplements regularly. Nevertheless, many still have intakes below the reference value.

Source

Beitz R, Mensink GBM, Fischer B, Thamm M. Vitamins—dietary intake and intake from dietary supplements in Germany. Eur J Clin Nutr 2002; 56: 539–545.