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How much folic acid is good for your heart?

Editorial

Many experts today warn that the risk of developing a circulatory disorder (thrombosis, stroke, heart attack, dementia, etc.) is increased in people with high blood levels of total homocysteine. Homocysteine is formed during the metabolism of the amino acid methionine, Normally, its concentration stays very low in the circulation since it is recycled back to methionine by a reaction dependent on folic acid and vitamin B12 or it is broken down and excreted.

However, under certain circumstances, for example in people whose diet is deficient in some vitamins, people with impaired kidney function or those affected by a genetic mutation of an enzyme that increases their folic acid

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requirement, homocysteine accumulates in the blood, and becomes involved in mechanisms that damage the blood vessels.

One of the strategies proposed to lower homocysteine levels is to ensure an adequate intake of folic acid and vitamin B12. Until recently, though, it was not clear how much an “adequate” intake was. Now, an international group of specialists (the Homocysteine Lowering Trialists’ Collaboration; see summary below) has investigated the homocysteine-lowering effects of different doses.

It found that 0.8, 2.0 and 5.0 mg folic acid all had the same effect, reducing plasma homocysteine levels by about 24%. By taking 0.4 mg vitamin B12 (a dose that cannot be obtained from dietary sources alone) at the same time, patients could achieve a further 7% reduction, but vitamin B6 had little effect. A reduction of 28–30% is usually enough to reach a normal homocysteine level. An interesting finding was that supplementation had the strongest effect in women and people with the highest initial homocysteine levels and poorest folate status.

In another major study (Vitamin Intervention for Stroke Prevention trial; see page 3) failure to respond to supplementation was found to be mainly due to specific medical conditions (malabsorption of vitamin B12, poor kidney function). The investigators suggest that, to overcome the first of these conditions, elderly people may need to take up to 1 mg vitamin B12 daily to reach adequate blood levels. People with kidney failure will need alternative treatments.

Based on these findings, it might be possible for people with elevated homocysteine levels to improve their status and help to keep their heart healthy by taking a supplement containing at least 0.8 mg folic acid and 0.4 mg vitamin B12.

A. Bowley, Editor

PREVENTION OF CARDIOVASCULAR DISEASE


Higher dose of folic acid needed to reduce homocysteine levels

Review

To establish the lowest dose of folic acid that has the maximum effect on plasma homocysteine levels, the Homocysteine Lowering Trialists’ Collaboration conducted a meta-analysis of 25 randomized, controlled trials involving 2596 subjects. The results are shown in the table below:

Folic acid dose (mg)	0.2	0.4	0.8	2.0	5.0
Reduction in homocysteine (%)	13	20	23	23	25

An additional 7% reduction in homocysteine was achieved when folic acid was taken together with vitamin B12 (0.4 mg daily).

Continued 

Conclusion

Increasing the daily dose of folic acid above 0.8 mg does not have a significantly greater effect on plasma homocysteine levels, but combined supplementation with folic acid and vitamin B12 reduces levels more than folic acid alone.

Source

Homocysteine Lowering Trialists' Collaboration. Dose-dependent effects of folic acid on blood concentrations of homocysteine: a meta-analysis of the randomized trials. Am J Clin Nutr 2005; 82: 806–812.

Vitamin B12 dose critical for lowering homocysteine levels**Intervention**

Following the failure of their Vitamin Intervention for Stroke Prevention trial to show an effect of supplementation with folic acid, vitamin B6 and vitamin B12 on recurrence of stroke and other cardiovascular complications, Spence et al. reexamined the data after excluding patients likely to have B12 malabsorption, those with high baseline B12 levels, and those with significant renal impairment.

In this subgroup of 2155 patients, they found a 21% risk reduction in the high-dose group (2.5 mg folic acid, 25 mg vitamin B6, 0.4 mg vitamin B12 daily) compared with the low-dose group (0.02 mg folic acid, 0.2 mg vitamin B6, 0.006 mg vitamin B12). Patients on the high-dose supplement whose baseline B12 status was above the median level had the best overall outcome.

Conclusion

The response of total homocysteine to vitamin supplementation was largely dependent on vitamin B12 status. Higher doses of B12 will be required to reduce homocysteine levels and lower the risk of recurrent stroke. Treatment to lower homocysteine should no longer be called “folate therapy”.

Source

Spence J, Bang H, Chambless LE, Stampfer MJ. Vitamin Intervention for Stroke Prevention trial: an efficacy analysis. Stroke 2005; 36: 2404–2409.

NUTRITION IN PREGNANCY AND LACTATION**Antioxidants delay premature delivery****Intervention**

Premature rupture of membranes is a common complication of pregnancy and a major contributor to neonatal morbidity and mortality. To investigate the value of antioxidant supplementation in such cases, Borna et al. gave 30 women admitted to hospital with preterm premature rupture of membranes 500 mg/day vitamin C and 400 IU/day vitamin E until delivery. Thirty comparable women received a placebo.

Continued 

Supplementation did not reduce the prevalence of complications (early sepsis, respiratory distress syndrome and neonatal death) significantly, but prolonged the latency period until delivery (10.5 ± 5.2 days compared to 3.5 ± 4.0 days in the placebo group).

Conclusion

Supplementation with vitamins C and E of women with preterm premature rupture of membranes is associated with a longer latency before delivery. By slowing the destruction of collagen and fetal membranes it may reduce infection-related morbidity.

Source

Borna S, Borna H, Daneshbodie B. Vitamins C and E in the latency period in women with preterm premature rupture of membranes. Int J Gynaecol Obstet 2005; 90: 16–20.

Folate supplements still needed to lower NTD risk

Review

To see if pregnant women in the USA have a lower risk of neural tube defects (NTD) following mandatory fortification of grain products with folic acid, Dietrich et al. compared data from National Health and Nutrition Examination Surveys (NHANES) conducted before and after fortification began.

In the general population, mean serum folate levels increased from 11.4 nmol/L to 26.9 nmol/L, while mean red cell levels increased from 375 nmol/L to 590 nmol/L. In women of childbearing age, however, less than 10% reached the red cell level associated with a significant reduction in NTD risk (906 nmol/L).

Conclusion

Food fortification with folic acid raises folate levels to acceptable levels. However, women of childbearing age may still need to take a folic acid supplement to reduce the risk of neural tube defects to a minimum.


Source

Dietrich M, Brown CJP, Block G. The effect of folate fortification of cereal-grain products on blood folate status, dietary folate intake, and dietary folate sources among adult non-supplement users in the United States. J Am Coll Nutr 2005; 24: 266–274.

Daily intake of 10'000 IU vitamin A without risk

Intervention

Vitamin A deficiency as well as excessive intakes of the vitamin are associated with an increased risk of congenital malformations. Data on the amount that is safe for pregnant women to take, however, are still conflicting. To improve knowledge about the safety of vitamin A in early pregnancy, Hartmann et al. determined exposure to retinol, retinol esters and their main metabolites in three groups of twelve nonpregnant women of childbearing age given 4'000, 10'000 or 30'000 IU vitamin A daily for 21 days.

Continued 

	<p>The area under the plasma concentration-time curve (AUC_{24h}), which served as indicator for exposure, showed a linear increase with dose for retinyl esters, but no change for retinol. Plasma concentrations of all-trans retinoic acid were at their highest 3 hours after dosing, fell below predose levels after 5 hours, and returned to predose levels at 16 hours. AUC_{24h} was similar for all doses. AUC_{24h} for 13-cis retinoic acid and 13-cis-4-oxo retinoic acid (established teratogenic metabolites) increased linearly with dose. At the highest dose, repeated doses caused a 25% increase in exposure.</p>
Conclusion	<p>The results confirm the current opinion that pregnant women can take a daily supplement of 10'000 IU vitamin A without increasing the risk of malformations in their unborn infant. Safe doses are probably even higher than 30'000 IU.</p>
Source	<p><i>Hartmann S, Brørs O, Bock J, et al. Exposure to retinyl esters, retinol, and retinoic acids in non-pregnant women following increasing single and repeated oral doses of vitamin A. Ann Nutr Metab 2005; 49: 155–164.</i></p>

PREVENTION OF CANCER

Vitamin E and beta-carotene protect some men against prostate cancer

Survey	<p>To establish the effect of supplementation with vitamin E, vitamin C or beta-carotene on the risk of prostate cancer, Kirsh et al. evaluated the questionnaires of 29'361 men participating in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. After up to eight years of follow-up, 1338 cases of prostate cancer were diagnosed.</p> <p>They found no association between cancer risk and intakes of these micronutrients overall. In smokers, however, long-term use of vitamin E supplements reduced cancer risk significantly. Supplementation with at least 2.0 mg beta-carotene daily was also associated with a reduced risk in men with low dietary intakes.</p>
Conclusion	<p>The results do not support population-wide supplementation with antioxidant micronutrients to prevent prostate cancer. However, male smokers could benefit from vitamin E supplementation, and men with low dietary intakes of beta-carotene could benefit from beta-carotene supplementation.</p>
Source	<p><i>Kirsh VA, Hayes RB, Mayne ST, et al. Supplemental and dietary vitamin E, beta-carotene, and vitamin C intakes and prostate cancer risk. J Natl Cancer Inst 2006; 98: 245–254.</i></p>

Carotenoid supplements reduce oxidative cell damage

Intervention

The development of cancer and cardiovascular diseases is thought to involve oxidative damage that can be minimized by an appropriate diet. To compare the protective effects of major dietary carotenoids, Zhao et al. randomly assigned 37 healthy postmenopausal women to a daily supplement containing 12 mg of either lutein, beta-carotene or lycopene, a combination containing 4 mg of each carotenoid or a placebo.

After eight weeks of supplementation, all the groups taking a carotenoid supplement had significantly lower levels of endogenous DNA damage than at baseline. In the mixed carotenoid and beta-carotene groups, the effect was apparent already after fifteen days.

Conclusion

These results suggest that carotenoid supplementation has beneficial effects in older women. It should therefore be considered as part of a protective strategy to minimize oxidative damage in vulnerable populations such as the elderly.

Source

Zhao X, Aldini G, Johnson EJ, et al. Modification of lymphocyte DNA damage by carotenoid supplementation in postmenopausal women. Am J Clin Nutr 2006; 83: 163–169.

NUTRITION AND EYE HEALTH

Age-related macular degeneration: Antioxidant benefits due to effect on cysteine homeostasis?


Intervention

The Age-Related Eye Disease Study (AREDS; first reported in 1999) demonstrated that supplementation with antioxidants and zinc reduced the risk of progression to advanced age-related macular degeneration in individuals at high risk. To elucidate possible mechanisms for this finding, Moriarty et al. analysed parameters of the endogenous antioxidant system (plasma glutathione, glutathione disulfide, cysteine, cystine and associated redox potentials) in a subset of the original collective at two time points (on average 1.7 and 6.7 years after enrollment).

At the first sampling, findings in both groups (with and without antioxidant supplementation) were similar. At the second sampling, plasma cysteine concentrations were significantly higher, and cysteine redox potential was lower in the antioxidant group.

Conclusion

These results suggest that strategies to reduce oxidative stress, by targeting cysteine concentrations and systems that regulate cysteine homeostasis, may provide additional benefits for preventing age-related macular degeneration, and slowing its progression.

Continued 

Source

Moriarty CSE, Adkison J, Lynn M, et al. Antioxidant supplements prevent oxidation of cysteine/cystine redox in patients with age-related macular degeneration. Am J Ophthalmol 2005; 140: 1020–1026.

NUTRITION AND BONE HEALTH

Vitamin D supplementation prevents falls in elderly**Intervention**

The risk of falling, with subsequent bone fracture, is greater in old age. A reason for this could be impaired neuromuscular function, caused by a vitamin D deficiency. Flicker et al. measured the effect of vitamin D supplementation on falling in 625 residents of assisted living facilities and nursing homes (mean age 83 and vitamin D status in lower normal range). Participants were assigned to vitamin D supplementation (initially 10'000 IU weekly; changed to 1000 IU daily during the trial) or placebo for two years. All participants took a supplement containing 600 mg calcium daily.

Nursing staff recorded falls in 170 (54%) of the supplemented group and 185 (59%) of the placebo group. Bone fractures occurred in 25 and 35 people in the respective groups.

Conclusion

Elderly residents of nursing homes can lower their risk of falling by regular intake of a vitamin D supplement, even if they are not vitamin D deficient.

Source

Flicker L, MacInnis RJ, Stein MS, et al. Should older people in residential care receive vitamin D to prevent falls? Results of a randomized trial. J Am Geriatr Soc 2005; 53: 1881–1888.

THERAPEUTIC APPLICATIONS

Supplementation speeds healing of pressure sores**Intervention**

To measure the healing effect of supplementation with arginine, vitamin C and zinc in patients with pressure ulcers, Desneves et al. randomly assigned 16 patients to one of three diets: A - the standard hospital diet; B - diet A plus a high-protein/high-energy supplement; C – diet A plus a high-protein/high-energy supplement containing 9 g arginine, 500 mg vitamin C and 30 mg zinc. Pressure ulcer severity was assessed before treatment and after 1, 2 and 3 weeks.

Continued 

A clinically significant improvement in healing occurred in patients on diet C already after two weeks; patients on diet A showed a small improvement after three weeks; those on diet B showed no improvement.

Conclusion

Use of a nutritional supplement containing arginine, vitamin C and zinc could significantly lower the costs associated with management of pressure sores, as well as reducing patient discomfort. The results of this small study need to be confirmed in a larger number of patients.

Source

Desneves KJ, Todorovic BE, Cassar A, Crowe TC. Treatment with supplementary arginine, vitamin C and zinc in patients with pressure ulcers: a randomised controlled trial. Clin Nutr 2005; 24: 979–987.

Heart patients benefit from arginine supplements

Intervention

The amino acid L-arginine is the biological precursor of nitric oxide, which is involved in cardiovascular protective mechanisms. To evaluate the clinical potential of arginine, Yin et al. conducted an open, crossover study in 31 patients with stable coronary artery disease. Patients first received 5 mg arginine or 250 mg vitamin C twice daily for four weeks. After a two-week washout period, the alternative treatment was given for a further four weeks. Before and after each treatment, endothelial function and inflammatory markers were measured in all patients. The susceptibility of low-density lipoprotein (LDL) particles to oxidation was also measured in 11 of the patients before and after treatment with L-arginine.

Both treatments significantly improved brachial artery flow-mediated dilatation (a sign of improved endothelial function), but did not improve lipid profiles or circulating levels of inflammatory markers. The susceptibility of LDL particles to oxidation improved by 27% after arginine supplementation.

Conclusion

Oral supplementation with L-arginine improved endothelial function and reduced LDL oxidation in patients with stable coronary artery disease.


Source

Yin WH, Chen JW, Tsai C, et al. L-arginine improves endothelial function and reduces LDL oxidation in patients with stable coronary artery disease. Clin Nutr 2005; 24: 988–997.

Supplements improve life quality in lung cancer patients

Survey

To find out if supplementation with vitamins and minerals improves survival and quality of life of patients suffering from non-small cell lung cancer, Jatoi et al. evaluated the results of a survey on 1129 patients (714 supplement users, 415 non-users).

Continued 

Supplement users had a median survival of 4.3 years; non-users had a median survival of 2.0 years. Supplement users scored better on the Lung Cancer Symptom Scale (a validated instrument designed to evaluate major symptoms in lung cancer patients) than non-users.

Conclusion

Patients with non-small cell lung cancer who used vitamin/mineral supplements lived longer and had a significantly better quality of life than those who did not, also after adjusting for related variables.

Source

Jatoi A, Williams B, Nichols F, et al. Is voluntary vitamin and mineral supplementation associated with better outcome in non-small cell lung cancer patients? Results from the Mayo Clinic lung cancer cohort. Lung Cancer 2005; 49: 77–84.

Supplementation can improve diabetics' kidney function

Intervention

Impaired kidney function is a serious complication of type 2 diabetes. To assess the effects of micronutrient supplementation on kidney pathology in diabetes, Farvid et al. randomly assigned 69 patients to three months supplementation with 200 mg magnesium and 50 mg zinc (Group M), 200 mg vitamin C and 100 IU vitamin E (Group V), both minerals and vitamins (Group MV) or placebo (Group P), and measured parameters of early nephropathy before and after treatment.

After three months, urinary excretion of albumin (indicator of glomerular dysfunction) was significantly lower in Groups V and MV. Group MV also showed significant reductions in blood pressure, fasting blood glucose and serum malondialdehyde (a product of lipid peroxidation), and increases in the beneficial components of cholesterol HDL and ApoA1.

Conclusion

Supplementation with vitamins C and E, together with magnesium and zinc, improved glomerular function (but not tubular function) in patients with type 2 diabetes.

Source

Farvid MS, Jalali M, Siassi F, Hosseini M. Comparison of the effects of vitamins and/or mineral supplementation on glomerular and tubular dysfunction in type 2 diabetes. Diabetes Care 2005; 28: 2458–2464.