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Higher requirements of calcium and vitamin D for bone health?

Editorial

The American Food and Nutrition Board published in 1997 their recommendations for the intake of vitamin D and calcium. Vitamin D is provided by either diet or by a sunlight dependent synthesis that is markedly diminished or absent in the winter. Therefore, people living in the northern (> 40°N) latitude, that includes most of Europe, can easily become vitamin D deficient. To cover the needs of adults independently of exposure to sunlight, the adequate intake (AI)

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has been set at 5.0 µg/day for men and women up to an age of 50 years. This value has been doubled at 10 µg/day for the age group 51 to 70 years considering bone loss as an indicator of adequacy. Elderly above 70 years should even increase their intake to 15 µg/day.

The AI for calcium has been set at 1000 mg/day for men and women between 19 and 50 years. Since calcium retention falls with advancing age and the requirement for bone metabolism might be higher, the AI for adults above 50 years has been increased to 1200 mg/day. In the EU, however, the recommended daily calcium intake is as low as 700 mg and the daily vitamin D intake 0-10 µg (EU PRI 1993; [tables 1 and 2; KD Cashman p 6]).

99% of calcium is found in mineralized tissues like bones and its metabolism depends on a sufficient vitamin D supply. It is proposed that the plasma concentration of 25-hydroxyvitamin D was higher during the evolution when sun exposure was higher. A level below 50 nmol/L may well increase the risk for many chronic diseases such as cardiovascular disease, hypertension, diabetes mellitus, inflammatory diseases and even cancer. A meta-analysis (page 5) found an association between the intake of vitamin D supplements and a decrease in total mortality rates.

The most important consequence of vitamin D and calcium deficiencies is, however, the increased risk of osteoporosis. In Europe, one out of eight women over 50 will experience a fracture of a vertebra during her lifetime. Osteoporosis patients occupy over 500,000 bed-days in hospitals. This will probably double during the next 50 years. All bone fractures generated in 2003 in the EU a cost of over 25 billion euros (G. Finkenstedt. *J Miner Stoffwechs* 2007; 14 (3): 93–98).

Another meta-analysis (page 5) combined data from 29 randomized trials using calcium or calcium plus vitamin D supplements in people aged 50 years or older to prevent fractures and osteoporotic bone loss. The treatment was associated with a reduced rate of bone loss at the hip and in the spine. A minimum dose of 1200 mg calcium per day and of 20 µg vitamin D has been proposed as a consequence of this analysis.

Therefore, plasma levels of 25-hydroxyvitamin D and calcium should be measured as a matter of routine in people 50 years and above. This would allow to evaluate whether additional supplements are required that could contribute to the risk reduction for chronic diseases as well as of health care costs.

ANTI-INFLAMMATORY PROPERTIES OF NUTRIENTS

Selenium, glutamine and eicosapentaenoic acid have demonstrated clinical benefits

Review

The current knowledge about oxidative stress-related organ dysfunction in inflammatory and septic conditions is reviewed with regard to potential prevention and treatment by antioxidants in critically ill patients. The focus is directed on naturally occurring antioxidants used in clinical trials.

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PubMed, Medline, and personal databases have been searched for respective clinical trials.

Plasma concentrations of antioxidant micronutrients are depressed during critical illness and especially during sepsis. The causes of these low levels include losses with biological fluids, low intakes, dilution by resuscitation fluids, as well as systemic inflammatory response syndrome-mediated redistribution of micronutrients from plasma to tissues. Numerous clinical trials have been conducted showing beneficial effects of supplementation. Interestingly, among the candidates, glutamine, glutathione, and selenium are linked to the potent glutathione peroxidase enzyme family at some stage of their synthesis and metabolism.

Conclusion

Three antioxidant nutrients have demonstrated clinical benefits and reached level A evidence: a) selenium improves clinical outcome (infections, organ failure); b) glutamine reduces infectious complication in large-sized trials; and c) the association of eicosapentaenoic acid and micronutrients has significant anti-inflammatory effects. Other antioxidants are still on the clinical benchmark level, awaiting well-designed clinical trials.

Source

Berger MM, Chioloro RL. Antioxidant supplementation in sepsis and systemic inflammatory response syndrome. *Crit Care Med.* 2007 Sep;35(9 Suppl):S584-90.

FOLIC ACID TO LOWER HOMOCYSTEINE

Hyperhomocysteinemia linked to neurodegenerative diseases

Review

Neuropsychiatric diseases cause enormous health care costs worldwide. A link between hyperhomocysteinemia (HHcy) and neurodegenerative diseases has first been described in patients with a deficiency of the enzyme cystathionine- β -synthase. Epidemiological studies have shown a dose-dependent relationship between concentrations of homocysteine (Hcy) and the risk of neurodegenerative diseases. Elevated concentration of Hcy is a marker for B-vitamin deficiency (folate, B12, B6). HHcy causes hypomethylation which is an important mechanism that links Hcy to dementia. Supplementation with B-vitamins aims at reducing the risk of neurodegenerative diseases. Current evidence suggests that Hcy-lowering treatment has a positive effect for the secondary and primary prevention of stroke. HHcy is very common in patients with Parkinson disease, particularly those who receive L-dopa treatment. Furthermore, a positive association has been reported between HHcy and multiple sclerosis. Moreover, HHcy and vitamin B deficiency are reported to have a causal role in depression, and epilepsy. In addition several anti-epileptic drugs cause secondary HHcy. Therefore, sufficient intakes of the vitamins are recommended for patients who have already developed neuropsychiatric diseases. Vitamin B deficiency should be suspected in children with development disorders, failure to thrive and unexplained neurological manifestations. Elderly people are also an important at-risk group where vitamin B deficiency and HHcy have been linked to neurodegenerative diseases. Treatment with folate, B12, and B6 can improve cerebral function. Preventive vitamin B supplementation and sufficient intake seem very im-

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portant for secondary and primary prevention of neuropsychiatric disorders, especially in subjects with a low intake or status of the vitamins.

Conclusion

Hyperhomocysteinemia is linked to an increased risk for neurodegenerative diseases, especially in the aging population, and predict a decline in cognitive functions. Therefore, homocysteine levels should be measured in elderly persons as part of the risk profile. Hcy concentrations above 12 $\mu\text{mol/L}$ should be treated by supplementation with the B-vitamins folate, vitamin B12, and vitamin B6.

Source

Herrmann W, Lorenzl S, Obeid R. Review of the role of hyperhomocysteinemia and B-vitamin deficiency in neurological and psychiatric disorders. Current evidence and preliminary recommendations. *Fortschr Neurol Psychiatr.* 2007; 75: 515-27

Reduced folate status can be corrected by supplements or fortification

Review

Severe folate deficiency that causes specific macrocytic megaloblastic anemia is not common in developed countries. However, even marginal deficiency is associated with an increased risk of neural tube defects (proven), ischemic heart disease and stroke (probable), certain cancers and decline in cognitive function (possible). Dietary supply of folate does usually not satisfy the generally recommended intake of 400 μg per day since the natural folate is chemically very unstable. Furthermore, during harvesting, distribution, storage and processing severe losses occur. Finally, the natural folate is not fully bioavailable resulting in a reduced folate status. From several studies it is clear, that efforts to increase the status by improving dietary intakes is difficult. Dietary advice is totally ineffective as well as providing an extra 400 $\mu\text{g/day}$ of food folate. Diets containing an extra 400 μg of folic acid per day in form of fortified foods significantly increase the red cell folate status, but the most successful regime is the addition of a supplement of 400 $\mu\text{g/day}$. At this level, masking of pernicious anemia caused by vitamin B12 deficiency will not occur. The antifolate Methotrexate is an effective anti-cancer-drug. It can, therefore, be postulated that high levels of folic acid could accelerate the growth of tumors. So far, there is no observation supporting this rather theoretical concern. But the combined intake from fortified food and from supplements should not exceed the upper tolerable level of intake (UL) defined by the EFSA.

Conclusion

Inadequate folate intake is still very common in most countries despite more intense professional dietary advice. Since more than half of pregnancies are unplanned, mandatory food fortification would be the best choice. However, the level of fortification is usually suboptimal for the prevention of neural tube defects; therefore, the advice to take supplements should persist. Supplements of folic acid at the population reference intake of 400 $\mu\text{g/day}$ are safe as judged by decades of use in many populations. They normalize the risk associated with deficiency such as neural tube defects, ischemic heart disease, stroke, certain cancers and a decline in cognitive functions.

Source

Scott JM. Reduced folate status is common and increases disease risk. It can be corrected by daily ingestion of supplements or fortification. *Novartis Found Symp.* 2007;282:105-17; discussion 117-22, 212-8.

Calcium and Vitamin D supplements to prevent osteoporotic risks

Meta-analysis

A meta-analysis has been performed to answer the question whether supplementation of calcium or calcium plus vitamin D can reduce the risk for osteoporotic fractures. 29 randomized trials with 63,897 persons have been combined. These included people aged 50 years or older. The main outcomes were fractures of all types and percentage change of bone-mineral density from baseline. Data were pooled by use of a random-effect model. In trials that reported fracture as an outcome (17 trials, n=52,625), treatment was associated with a 12% risk reduction in fractures of all types (risk ratio 0.88, 95% CI 0.83-0.95; p=0.0004). In trials that reported bone-mineral density as an outcome (23 trials, n=41,419), the treatment was associated with a reduced rate of bone loss of 0.54% (0.35-0.73; p<0.0001) at the hip and 1.19% (0.76-1.61%; p<0.0001) in the spine. The fracture risk reduction was significantly greater (24%) in trials in which the compliance rate was high (p<0.0001). The treatment effect was better with calcium doses of 1200 mg or more than with doses less than 1200 mg (0.80 vs. 0.94; p=0.006), and with vitamin D doses of 800 IU (20 µg) or more than with doses less than 800 IU (0.84 vs. 0.87; p=0.03).

Conclusion

The outcome of this analysis supports the use of calcium, or calcium in combination with vitamin D supplementation, in the preventive treatment of osteoporosis in people aged 50 years or older. For best therapeutic effect, minimum doses of 1200 mg of calcium, and 800 IU (20 µg) of vitamin D (for combined calcium plus vitamin D supplementation) are recommended.

Source

Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. *Lancet*. 2007; 370:657-66. Comment in: *Lancet*. 2007; 370:632-4.

Vitamin D supplements associated with decrease in total mortality

Meta-analysis

Ecological and observational studies suggest that low vitamin D status could be associated with higher mortality from life-threatening conditions including cancer, cardiovascular disease, and diabetes mellitus that account for 60% to 70% of total mortality in high-income countries. The risk of dying from any cause in subjects who participated in randomized trials testing the impact of vitamin D supplementation (vitamin D₂ and vitamin D₃) on any health condition has been examined. 18 independent randomized controlled trials, including 57,311 participants have been identified. A total of 4,777 deaths from any cause occurred during a trial size-adjusted mean of 5.7 years. Daily doses of vitamin D supplements varied from 300 to 2000 IU (7.5 to 50 µg). The trial size-adjusted mean daily vitamin D dose was 528 IU (13.2 µg). In 9 trials, there was a 1.4- to 5.2-fold difference in serum 25-hydroxyvitamin D between the intervention and control groups. The summary relative risk for mortality from any cause was 0.93 (95% confidence interval, 0.87-0.99). There was neither indication for heterogeneity nor indication for publication biases. The summary relative risk did not change according to the addition of calcium supplements in the intervention.

Conclusion

Intake of ordinary doses of vitamin D supplements seems to be associated with decreases in total mortality rates. The relationship between baseline vitamin D status, dose of vitamin D supplements, and total mortality rates remains to be investigated. Population-based, placebo-controlled randomized trials with total mortality as the main end point should be organized for confirming these findings.

Source

Autier P, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. *Arch Intern Med.* 2007 Sep 10;167(16):1730-7.

Dietary vitamin D intake by European populations is not sufficient**Review**

Calcium is required for normal growth and development as well as maintenance of the skeleton. Vitamin D is also essential for intestinal calcium absorption and plays a central role in maintaining calcium homeostasis and skeletal integrity. In addition, both micronutrients have important roles in non-skeletal-related physiological processes. Of concern, significant proportions of some population groups fail to achieve the recommended calcium intakes in a number of western countries. Furthermore, while cutaneous biosynthesis upon exposure of skin to ultraviolet B light is the major source of vitamin D for most people, this does not occur during winter time. Thus, there is an increased reliance on dietary sources during winter months to help maintain adequate vitamin D status. Since vitamin D is found naturally only in a limited number of foods, the usual dietary vitamin D intake by many European populations is not sufficient to maintain adequate vitamin D status. As a consequence, considering the cut-off value of 25-hydroxyvitamin D at 50 nmol/L, the prevalence of vitamin D deficiency was 85 % in Irish female adolescents and between 33 and 64% in men and women during winter months. For both, calcium and vitamin D upper tolerable intake levels have been defined. For vitamin D, adverse effects may occur at plasma levels of 25-hydroxyvitamin D above 200 nmol/L.

Conclusion

Suboptimal intakes and /or status of calcium and vitamin D are common in many individuals. Nutritional supplements can certainly reduce the incidence of these nutritional deficiencies, but some consideration is needed in relation to the minimum effective dose of these micronutrients. Calcium and vitamin D may also lower the risk of certain diseases, but again the issue of minimum effective dose is relevant. In general, it would appear that the levels of supplementation which bring about reduction in disease risk are higher than those presently included in many supplements. Further research is needed to evaluate the effective dose while ensuring safety. In general, the level of inclusion of calcium and vitamin D in supplements at present appears to be sufficient so as not to place individuals at risk of excessive intake.

Source

Cashman KD. Calcium and vitamin D. *Novartis Found Symp.* 2007;282:123-38; discussion 138-42, 212-8.

VITAMIN E TO LOWER VENOUS THROMBOEMBOLISM**Vitamin E supplements to reduce the risk of venous thromboembolism****Intervention**

Supplementation with vitamin E may antagonize vitamin K in healthy adults, but it is unclear whether intake of vitamin E decreases the risk of venous thromboembolism (VTE). The Women's Health Study randomized 39,876 women ≥ 45 years of age to receive 600 IU of natural source vitamin E or placebo on alternate days. Before randomization, 26,779 participants gave blood samples, which were used to determine factor V Leiden, G20210A prothrombin, and 677C>T MTHFR polymorphisms. Documented VTE (including deep vein thrombosis or pulmonary embolism) and unprovoked VTE (no recent surgery, trauma, or cancer diagnosis) were prospectively evaluated, secondary end points of the trial. During a median follow-up period of 10.2 years, VTE occurred in 482 women: 213 in the vitamin E group and 269 in the placebo group, a significant 21% hazard reduction (relative hazard, 0.79; 95% CI, 0.66 to 0.94; $P=0.010$). For unprovoked VTE, the hazard reduction was 27% (relative hazard, 0.73; 95% CI, 0.57 to 0.94; $P=0.016$). In subgroup analyses, the 3% of participants who reported VTE before randomization had a 44% hazard reduction (relative hazard, 0.56; 95% CI, 0.31 to 1.00; $P=0.048$), whereas women without prior VTE had an 18% hazard reduction (relative hazard 0.82; 95% CI, 0.68 to 0.99; $P=0.040$). Women with either factor V Leiden or the prothrombin mutation had a 49% hazard reduction associated with vitamin E treatment (relative hazard, 0.51; 95% CI, 0.30 to 0.87; $P=0.014$).

Conclusion

These data suggest that supplementation with vitamin E may reduce the risk of venous thromboembolism in women, and those with a prior history or genetic predisposition may particularly benefit.

Source

Glynn RJ, Ridker PM, Goldhaber SZ, Zee RY, Buring JE. Effects of random allocation to vitamin E supplementation on the occurrence of venous thromboembolism: report from the Women's Health Study. *Circulation*. 2007 Sep 25;116(13):1497-503.

MAINTAINING GOOD HEALTH AFTER THE AGE OF 50**A combination of multivitamin, calcium and omega-3 fatty acids to compensate for inadequate dietary intake****Review**

The objective of this review is to enhance the pharmacist's ability to recognize and make treatment recommendations for the safe use of vitamins and supplements for an ambulatory, postmenopausal woman with cardiovascular disease. Literature reports were selected for their clinical relevance with emphasis on randomized, controlled trials, meta-analyses, cohort studies, and information from the American Heart Association and the Food and Nutritional Board of the Institute of Medicine. An outline was developed and literature reports were separated into the categories of vitamins, minerals, and supplements. The primary literature provided information for the use of vitamins, minerals, and supplements, which are popular with older women with chronic disease states. The results included current guidelines that have been established to assist in maintaining good health and to prevent disease in a

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specific population, those 51 years of age or older. Elderly women with a history of cardiovascular disease often have difficulties with calorie restriction and do not follow guidelines established by the food pyramid.

Conclusion

When dietary intake is inadequate and recommendations are not met through food choices, a combination of a vitamin preparation, calcium, and an omega-3 preparation can help maintain good health in older women with cardiovascular disease.

Source

Nykamp D, Kavanaugh ED, Wenker AP. Vitamins: the wise choice for women with cardiovascular disease. *Consult Pharm.* 2007 Jun;22(6):490-502.

NUTRITION AND NAIL HEALTH

Biotin or silicon, but not other vitamins, to abate brittle nail syndrome

Review

Nail health and appearance are global concerns. The use of biotin, vitamin E, vitamin C, vitamin A, retinoids, silicon, zinc, iron, copper, selenium, and vitamin B12 in nail health and disease has been investigated. Besides proper nail care that helps maintaining nail health, studies with biotin are most convincing. Clinical trials show a benefit treating brittle nail syndrome with biotin for at least 2 to 3 months. However, the optimal duration of the treatment has not been determined. Conflicting evidence exists for the use of vitamin E to treat yellow nail syndrome. Severe deficiencies of calcium, iron, and zinc negatively affect nail health; however, patients suffering from brittle nail syndrome usually have normal nail mineral levels. In a double-blind placebo controlled trial 10 mg of choline-stabilized orthosilic acid daily for 20 weeks significantly decreased nail brittleness.

Conclusion

Brittle nail syndrome can be improved by supplementation with a 2.5-mg dose of biotin daily or a 10-mg dose of silicon daily for a few months. Other vitamins or minerals fail to improve nail health.

Source

Scheinfeld N, Dahdah MJ, Scher R.J. Vitamins and minerals: their role in nail health and disease. *Drugs Dermatol.* 2007 Aug;6(8):782-7.

FISH OIL FOR CARDIOVASCULAR HEALTH

Docosahexaenoic acid to lower triacylglycerol and small, dense LDL particles

Intervention

In a double-blind, randomized, placebo-controlled parallel study hypertriglyceridemic men aged 39-66 y (n = 34) received for the first 8 days no supplements and then either 7.5 g DHA oil/d (3 g DHA/d) or olive oil (placebo) for the last 90 days. The concentrations of apoproteins; large, medium, and small VLDL, LDL, and HDL particles; and the mean diameters of these particles in

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fasting and postprandial plasma have been determined.

DHA supplementation for 45 d significantly ($P < 0.05$) decreased concentrations of fasting triacylglycerol (24%), large VLDL (92%), and intermediate-density lipoproteins (53%) and the mean diameter of VLDL particles (11.1 nm). It elevated concentrations of LDL cholesterol (12.6%), small VLDL particles (133%), and large LDL particles (120%) and the mean diameter of LDL particles (0.6 nm) in fasting plasma. Similar changes were observed for area under the curve for postprandial samples (0-6 h); however, the number of small dense LDL particles decreased significantly (21%), and the change in LDL cholesterol was not significant.

DHA supplementation lowered postprandial triacylglycerol concentration to the same degree as at baseline after the test breakfast at 2, 4, 6, and 8 hours. Neither HDL cholesterol nor the ratio total/HDL cholesterol changed. Continued supplementation with DHA beyond 45 days caused no further changes; placebo treatment altered none of the responses tested.

Conclusion

DHA supplementation may improve cardiovascular health by lowering concentrations of fasting and postprandial triacylglycerols and small, dense LDL-particles. DHA reduces atherogenic lipids and lipoproteins and increases concentrations of cardioprotective lipoproteins.

Source

Kelley DS, Siegel D, Vemuri M, Mackey BE. Docosahexaenoic acid supplementation improves fasting and postprandial lipid profiles in hypertriglyceridemic men. *Am J Clin Nutr.* 2007 Aug;86(2):324-33.

Fish oil supplements associated with improved endothelial function

Intervention

In a randomized, single-blinded, placebo-controlled trial, 26 subjects (17 men and 9 women; mean age 31 ± 3.7 years) received 1 g fish oil (FO) capsules ($n = 14$) or placebo (1 g of corn oil, $n = 12$) for 14 days. At day 0 and day 14, heart rate (HR), blood pressure, endothelium-dependent brachial artery flow-mediated vasodilation (EDV), and endothelium-independent nitroglycerin-mediated vasodilation (EIDV) were assessed with ultrasound. FO supplementation resulted in a significant increase in EDV ($20.4\% \pm 13.2\%$ vs. $9.9\% \pm 5.4\%$; $P = 0.036$) and EIDV ($32.6\% \pm 16.8\%$ vs. $18.0\% \pm 14.9\%$; $P = 0.043$). Resting HR decreased by a mean of 5.9 ± 9.4 bpm (FO) compared with placebo (mean increase of 0.73 ± 4.8 bpm [$P = 0.05$]). FO supplementation in healthy subjects is associated with improved endothelial function and decreased resting HR. No adverse side effects have been reported.

Conclusion

The study confirms that fish oil supplementation also improves the endothelial function of healthy subjects. This finding adds further evidence to the potentially cardioprotective effects of marine ω -3 fatty acids. Studies suggest that endothelial dysfunction may be the initiating event in the atherosclerotic process that subsequently leads to coronary artery disease. Although further large-scale studies need to be conducted, these findings may provide a mechanism to explain the reduced rates of coronary heart disease in populations that consume higher quantities of fish.

Source

Shah AP, Ichiuji AM, Han JK, Traina M, El-Bialy A, Meymandi SK, Wachsner RY. Cardiovascular and endothelial effects of fish oil supplementation in healthy volunteers. *J Cardiovasc Pharmacol Ther.* 2007 Sep;12(3):213-9.