

Whitehall-Robins Supplement

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A selection of recent findings in the field of nutrition

Randomized trial of folic acid supplementation and serum homocysteine levels.

High homocysteine levels could be lowered by folic acid. Lowering high homocysteine is expected to reduce heart disease mortality by about 15%. A recent meta-analysis demonstrated a maximum reduction of high homocysteine with a 1 mg dosage of folic acid, but the effect of lower doses is unclear. This randomized, double-blind, placebo-controlled trial tested 0.2, 0.4, 0.6, 0.8, and 1.0 mg/d of folic acid supplementation and its lowering effect on serum homocysteine in patients with known heart disease. The folic acid tablets were taken for 3 months. Median serum homocysteine decreased with increasing folic acid dosage and reached its maximum reduction ability at 0.8 mg of folic acid (23% reduction in homocysteine, which is comparable to the effect of folic acid dosages of 1 mg/d, and above). The higher an individual's baseline serum homocysteine, the greater the response to folic acid, however, there were statistically significant reductions regardless of the initial level. Serum homocysteine concentration returned to baseline 3 months after supplementation was stopped indicating that a sustained serum homocysteine reduction needs continued folic acid supplementation. The authors conclude "a dosage of folic acid of 0.8 mg/d appears necessary to achieve the maximum reduction in serum homocysteine level across the range of homocysteine levels in the population. Current US food fortification levels will achieve only a small proportion of the achievable homocysteine reduction". Similar folic acid food fortification levels are used in Canada.

[Wald DS, et al. Arch Intern Med 2001;161:695-700]

Low serum plasma folate concentrations are associated with low sperm density and count in male smokers and nonsmokers.

The role of folate in female reproductive function is well recognized, however, little is known about its role in male reproductive function. There are early indications that folate may be necessary for male reproductive function which is supported by the observation that folate antagonists can impair reproductive function in men. This observational study among smokers and nonsmokers measured blood levels of plasma folate and homocysteine, total seminal plasma concentration, non-methyl- and 5-methyltetrahydrofolate concentrations, and total sperm count and density. Total seminal plasma folate concentrations were on average 1.5 times higher than blood plasma folate concentrations in all men. Total and 5-methyltetrahydrofolate concentrations were significantly correlated with blood plasma folate and homocysteine. Seminal plasma non-methyltetrahydrofolate levels correlated significantly with sperm density and total sperm count. It is suggested that non-methyltetrahydrofolates might be required for spermatogenesis or the sperm maturation process. Seminal plasma of smokers contained a proportionally lower concentration of non-methyltetrahydrofolates compared with nonsmokers.

[Wallock LM, et al. Fert Steril 2001;75:252-259]

A high ratio of dietary animal to vegetable protein increases the rate of bone loss and the risk of fracture in postmenopausal women.

Diet is an important factor for bone health. Although the role of calcium is well recognized, the role of other nutrients such as protein, remains controversial. Different sources of dietary protein may have different effects on bone metabolism. Animal foods provide acid precursors, while vegetables and fruit contain not only amino acids but also base precursors not found in animal foods. Diets in industrialized countries are typically rich in animal foods and low in vegetable foods, which might lead to a dietary net acid load. Imbalance between dietary acid and base



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precursors lead to a negative effect on calcium balance. This calcium loss can lead to a decline in bone mineral content and bone mass. This prospective study investigated the hypothesis that a high dietary ratio of animal to vegetable foods increases the rate of bone loss and the risk of fracture. The study population comprised of 1035 white women aged >65 y. These women were followed for an average of 7 years. Protein intake was measured using a food-frequency questionnaire and bone mineral density was measured by dual-energy X-ray absorptiometry. In this study, bone mineral density was not significantly associated with the ratio of animal to vegetable protein intake. Women with a high ratio had a higher rate of bone loss at the femoral neck and nearly four times the risk of hip fracture compared to women with low ratio. The authors suggest that an increase in vegetable protein intake and a decrease in animal protein intake (i.e. lowering the animal/vegetable protein ratio) may decrease bone loss and the risk of hip fracture. This possibility needs to be confirmed in other prospective and randomized studies. [Sellmeyer DE, et al. *Am J Clin Nutr* 2001;73:118-122]

Efficacy and safety of vitamin D3 intake exceeding the lowest observed adverse effect level.

Recent guidelines recommended 2000 IU as the highest vitamin D intake that healthy adults can consume without risking hypercalcemia. Serum 25 (OH) D is recognized as the appropriate index reflecting vitamin D adequacy. Therefore, maintaining an adequate concentration of 25 (OH) D is desirable to suppress PTH and this suppression is believed to be beneficial for bone. Recent evidence indicates that an intake of at least 4000 IU of vitamin D3 may be required to ensure desirable 25 (OH) D concentrations. This Canadian study assessed the safety and efficacy of vitamin D3 intakes of 1000 IU and 4000 IU/d for 2-5 months in healthy Canadian men and women. The main results of this study were that although the 1000 IU/d intake offered reasonable assurance of a favorable effect on serum 25 (OH) D concentrations, it did not ensure that most subjects attained the desirable effect which was mostly achieved with 4000 IU/d intake of vitamin D3. Neither 1000 IU/d nor 4000 IU/d of vitamin D3 raised safety concerns. The authors conclude that the 4000 IU/d dosage "effectively increased 25 (OH) D to high-normal concentrations in practically all adults and serum 25 (OH) D remained within the physiologic range; therefore, we consider 4000 IU vitamin D3 to be a safe intake".

[Vieth R, et al. *Am J Clin Nutr* 2001;73:288-294]

Suggested readings

Relation among serum and tissue concentrations of lutein and zeaxanthin and macular pigment density.

[Johnson EJ, et al. *Am J Clin Nutr* 2000;71:1555-1562]

Primary prevention of coronary heart disease in women through diet and lifestyle.

[Stampfer MJ, et al. *N Engl J Med* 2000;343:16-22]

Secondary prevention with antioxidants of cardiovascular disease in endstage renal disease (SPACE): randomized placebo-controlled trial.

[Boaz M et al. *Lancet* 2000;356:1213-1218]

A prospective study of fruit and vegetable consumption and incidence of colon and rectal cancers.

[Michels KB, et al. *J Natl Cancer Inst* 2000;92:1740-1752]

Prospective study of major dietary patterns and risk of coronary heart disease in men.

[Hu FB, et al. *Am J Clin Nutr* 2000;72:912-921]

