

Health Benefits of Nutritional Supplements

Selected Abstracts

Compiled by

*Tim Wood, Ph.D.
Charles Hussey, M.S.*

*USANA Health Sciences
3838 West Parkway Blvd.
Salt Lake City, UT 84120*

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Forward

The importance of nutrition for human health has long been recognized. Prior to 1960, interest in this field largely focused on the etiology and prevention of acute nutrient deficiency diseases such as scurvy, rickets, and pellagra. Some 50 essential nutrients (vitamins, minerals, antioxidants, cofactors, essential amino acids, essential fatty acids) were identified, and recommended daily intakes for those essential nutrients (e.g. Recommended Dietary Allowances or RDAs) were developed. These recommendations, in turn, proved to be valuable in eradicating acute nutrient deficiency diseases.

During the past 20-30 years, attention has shifted to the role of diet and nutrition in the pathogenesis of chronic degenerative diseases. Heart disease, some cancers, osteoporosis, type II diabetes, and macular degeneration are all known to have dietary risk factors, many of which involve chronic nutrient deficiencies. Importantly, these associations have been much more difficult to study, in large measure because of the time frames involved. Chronic degenerative diseases develop over decades (lifetimes), and it is extremely challenging to conduct research programs for such extended periods. Nevertheless, advances in epidemiological and clinical research have helped us learn a great deal about the impacts (positive and negative) of diet and essential nutrient intakes on long-term health.

During the past decade, the scientific and healthcare communities have paid increasing attention to the role of nutritional supplements (as components of diet) in preventing and treating chronic disease. Hundreds of scientific studies have been conducted and published. These studies span a broad range of health issues. They have employed a wide variety of methodologies. And they have produced both positive and negative results. In some areas (e.g. the role of calcium and vitamin D supplements in slowing the progression of osteoporosis, and the role of folic acid supplements in preventing certain birth defects), results have been consistent, and benefits have been well accepted. In other areas (e.g. the role of antioxidant supplementation in preventing heart disease), results have been less consistent, and conclusions remain controversial. In any event, research on the health benefits of nutritional supplements is progressing, and evidence continues to mount that nutritional supplements offer a convenient and cost effective means for promoting health, over both the short- and long-terms.

The following is a collection of abstracts from about 100 scientific papers describing research on the health benefits of nutritional supplements. This collection is not exhaustive. Papers were selected on the basis of scientific merit and relevance to the field. The majority describes positive results, but in some, negative results are reported. Our objective in compiling this list was to provide readers with a good cross section of the scientific literature so that they could develop a sense for the current state of research in this field and draw their own conclusions concerning the role of supplementation in healthcare. References for many more papers are given in our bibliography entitled *Health Benefits of Nutritional Supplements: Selected Readings* .

For convenience, the abstracts have been sorted by health issue; namely Cardiovascular Health, Cancer Prevention, Strong Bones, Healthy Pregnancies/Healthy Babies, Sound Metabolism, Robust Immune Function, Acute Vision, and Other.

Other

The potential for dietary supplements to reduce premenstrual syndrome (PMS) symptoms.

Bendich A. 2000.
J Am Coll Nutr 19(1):3-12

Many types of dietary supplements have been advocated for the reduction of certain symptoms of premenstrual syndrome (PMS). However, only one supplement-calcium-has been demonstrated to be of significant benefit in a large, rigorous, double-blind, placebo-controlled trial. Limited evidence suggests that magnesium, vitamin E and carbohydrate supplements might also be useful, but additional research is needed to confirm these findings. Trials of vitamin B6 supplementation have had conflicting results, and high doses of this vitamin taken for prolonged periods of time can cause neurological symptoms. Trials of evening primrose oil have also had conflicting results; the two most rigorous studies showed no evidence of benefit. A variety of herbal products are suggested to reduce symptoms of PMS. The efficacy of these products is uncertain because of a lack of consistent data from scientific studies. Health professionals should be aware of the possible use of these supplements and ask those with PMS about their use of such products and counsel them based upon the totality of evidence.

Effect of an enteric-coated fish-oil preparation on relapses in Crohn's disease.

Belluzzi A, Brignola C, Campieri M, Pera A, Boschi S, Miglioli M. 1996.
N Engl J Med 334(24):1557-60

BACKGROUND: Patients with Crohn's disease may have periods of remission, interrupted by relapses. Because fish oil has antiinflammatory actions, it could reduce the frequency of relapses, but it is often poorly tolerated because of its unpleasant taste and gastrointestinal side effects. **METHODS:** We performed a one-year, double-blind, placebo-controlled study to investigate the effects of a new fish-oil preparation in the maintenance of remission in 78 patients with Crohn's disease who had a high risk of relapse. The patients received either nine fish-oil capsules containing a total of 2.7 g of n-3 fatty acids or nine placebo capsules daily. A special coating protected the capsules against gastric acidity for at least 30 minutes. **RESULTS:** Among the 39 patients in the fish-oil group, 11 (28 percent) had relapses, 4 dropped out because of diarrhea, and 1 withdrew for other reasons. In contrast, among the 39 patients in the placebo group, 27 (69 percent) had relapses, 1 dropped out because of diarrhea, and 1 withdrew for other reasons (difference in relapse rate, 41 percentage points; 95 percent confidence interval, 21 to 61; $P < 0.001$). After one year, 23 patients (59 percent) in the fish-oil group remained in remission, as compared with 10 (26 percent) in the placebo group ($P = 0.003$). Logistic-regression analysis indicated that only fish oil and not sex, age, previous surgery, duration of disease, or smoking status affected the likelihood of relapse (odds ratio for the placebo group as compared with the fish-oil group, 4.2; 95 percent confidence interval, 1.6 to 10.7). **CONCLUSIONS:** In patients with Crohn's disease in remission, a novel enteric-coated fish-oil preparation is effective in reducing the rate of relapse.

Comparison of dietary calcium with supplemental calcium and other nutrients as factors affecting the risk for kidney stones in women.

Curhan GC, Willett WC, Speizer FE, Spiegelman D, Stampfer MJ. 1997.
Ann Intern Med 126(7):497-504

BACKGROUND: Calcium intake is believed to play an important role in the formation of kidney stones, but data on the risk factors for stone formation in women are limited. **OBJECTIVE:** To examine the association between intake of dietary and supplemental calcium and the risk for kidney stones in women. **DESIGN:** Prospective cohort study with 12-year follow-up. **SETTING:** Several U.S. states. **PARTICIPANTS:** 91,731 women participating in the Nurses' Health Study I who were 34 to 59 years of age in 1980 and had no history of kidney stones. **MEASUREMENTS:** Self-administered food-frequency questionnaires were used to assess diet in 1980, 1984, 1986, and 1990. The main outcome measure was incident symptomatic kidney stones. **RESULTS:** During 903,849 person-years of follow-up, 864 cases of kidney stones were documented. After adjustment for potential risk factors, intake of dietary calcium was inversely associated with risk for kidney stones and intake of supplemental calcium was positively associated with risk. The relative risk for stone formation in women in the highest quintile of dietary calcium intake compared with women in the lowest quintile was 0.65 (95% CI, 0.50 to 0.83). The relative risk in women who took supplemental calcium compared with women who did not was 1.20 (CI, 1.02 to 1.41). In 67% of women who took supplemental calcium, the calcium either was not consumed with a meal or was consumed with meals whose oxalate content was probably low. Other dietary factors showed the following relative risks among women in the highest quintile of intake compared with those in the lowest quintile: sucrose, 1.52 (CI, 1.18 to 1.96); sodium, 1.30 (CI, 1.05 to 1.62); fluid, 0.61 (CI, 0.48 to 0.78); and potassium, 0.65 (CI, 0.51 to 0.84). **CONCLUSIONS:** High intake of dietary calcium appears to decrease risk for symptomatic kidney stones, whereas intake of supplemental calcium may increase risk. Because dietary calcium reduces the absorption of oxalate, the apparently different effects caused by the type of calcium may be associated with the timing of calcium ingestion relative to the amount of oxalate consumed. However, other factors present in dairy products (the major source of dietary calcium) could be responsible for the decreased risk seen with dietary calcium.

Putative analgesic activity of repeated oral doses of vitamin E in the treatment of rheumatoid arthritis. Results of a prospective placebo controlled double blind trial.

Edmonds SE, Winyard PG, Guo R, Kidd B, Merry P, Langrish-Smith A, Hansen C, Ramm S, Blake DR. 1997.
Ann Rheum Dis. 56(11):649-55

OBJECTIVE: Vitamin E, the most potent naturally occurring lipid soluble antioxidant has been suggested to possess both anti-inflammatory and analgesic activity in humans. This double blind and randomised study used a broad spectrum of clinical and laboratory parameters to investigate whether there was any additional anti-inflammatory or analgesic effects, or both, of orally administered alpha-tocopherol in rheumatoid arthritis patients who were already receiving anti-rheumatic drugs. **METHODS:** Forty two patients were enrolled and treated with alpha-tocopherol (n = 20) at a dose of 600 mg twice a day (2 x 2 capsules) or with placebo (n = 22) for 12 weeks. The following parameters were measured: (1) Three clinical indices of inflammation--the Ritchie articular index, the duration of morning stiffness, and the number of swollen joints; (2) three measures of pain--pain in the morning, pain in the evening, and pain after chosen activity; (3) haematological and biochemical measures of inflammatory activity; (4) assays for the oxidative modification of proteins and lipids. **RESULTS:** All laboratory measures of inflammatory activity and oxidative modification were unchanged. Furthermore, the clinical indices of inflammation were not influenced by the treatment. However, the pain parameters were significantly decreased after vitamin E treatment when compared with placebo. **CONCLUSION:** The results provide preliminary evidence that vitamin E may exert a small but significant analgesic activity independent of a peripheral anti-inflammatory effect, but which complements standard anti-inflammatory treatment.

Magnesium for the treatment of nocturnal leg cramps: a crossover randomized trial.

Frusso R, Zarate M, Augustovski F, Rubinstein A. 1999.
J Fam Pract 48(11):868-71

BACKGROUND: Nocturnal leg cramps are a common health problem in the ambulatory setting. Our objective was to evaluate the efficacy of magnesium in the treatment of nocturnal leg cramps. **METHODS:** Our study was a crossover randomized double-blind placebo-controlled trial. We included patients from a large university-based ambulatory clinic in Buenos Aires, Argentina, with at least 6 cramps during the previous month. A total of 93 subjects took part in a 4-week washout period with placebo. Those who were still eligible (n = 45) were randomized to receive either (1) an oral dose of 900 mg magnesium citrate twice daily for 1 month, followed by a matching placebo for 1 month, or (2) the placebo first, followed by magnesium. Both groups had a 4-week washout period with placebo between each treatment month. Forty-two patients completed the 4-month study. The main outcome was the number of nocturnal leg cramps, and the secondary outcomes were duration, severity, and sleep disorders caused by those cramps. **RESULTS:** There were no significant differences between magnesium and placebo in any of the evaluated outcomes. The mean number of cramps was 11.1 (standard deviation [SD] +/- 7.3) for placebo versus 11.8 (SD +/- 7.6) for magnesium (P = .59). We observed a significant period-effect bias: All patients improved over time regardless of the treatment sequence they received. **CONCLUSIONS:** Magnesium was not effective for the treatment of nocturnal leg cramps. The period-effect bias probably occurred because of a combination of the natural history of this condition, a regression to the mean, and a true placebo effect.

n-3 fatty acid supplements in rheumatoid arthritis.

Kremer JM. 2000.
Am J Clin Nutr 71(suppl):349S-51S

Ingestion of dietary supplements of n-3 fatty acids has been consistently shown to reduce both the number of tender joints on physical examination and the amount of morning stiffness in patients with rheumatoid arthritis. In these cases, supplements were consumed daily in addition to background medications and the clinical benefits of the n-3 fatty acids were not apparent until they were consumed for > or =12 wk. It appears that a minimum daily dose of 3 g eicosapentaenoic and docosahexaenoic acids is necessary to derive the expected benefits. These doses of n-3 fatty acids are associated with significant reductions in the release of leukotriene B(4) from stimulated neutrophils and of interleukin 1 from monocytes. Both of these mediators of inflammation are thought to contribute to the inflammatory events that occur in the rheumatoid arthritis disease process. Several investigators have reported that rheumatoid arthritis patients consuming n-3 dietary supplements were able to lower or discontinue their background doses of nonsteroidal antiinflammatory drugs or disease-modifying antirheumatic drugs. Because the methods used to determine whether patients taking n-3 supplements can discontinue taking these agents are variable, confirmatory and definitive studies are needed to settle this issue. n-3 Fatty acids have virtually no reported serious toxicity in the dose range used in rheumatoid arthritis and are generally very well tolerated.

A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study.

Sano M, Ernesto C, Thomas RG, Klauber MR, Schafer K, Grundman M, Woodbury P, Growdon J, Cotman CW, Pfeiffer E, Schneider LS, Thal LJ. 1997.
N Engl J Med 336(17):1216-22

BACKGROUND: There is evidence that medications or vitamins that increase the levels of brain catecholamines and protect against oxidative damage may reduce the neuronal damage and slow the progression of Alzheimer's disease. **METHODS:** We conducted a double-blind, placebo-controlled, randomized, multicenter trial in patients with Alzheimer's disease of moderate severity. A total of 341 patients received the selective monoamine oxidase inhibitor selegiline (10 mg a day), alpha-tocopherol (vitamin E, 2000 IU a day), both selegiline and alpha-tocopherol, or placebo for two years. The primary outcome was the time to the occurrence of any of the following: death, institutionalization, loss of the ability to perform basic activities of daily living, or severe dementia (defined as a Clinical Dementia Rating of 3). **RESULTS:** Despite random assignment, the baseline score on the Mini-Mental State Examination was higher in the placebo group than in the other three groups, and this variable was highly predictive of the primary outcome ($P < 0.001$). In the unadjusted analyses, there was no statistically significant difference in the outcomes among the four groups. In analyses that included the base-line score on the Mini-Mental State Examination as a covariate, there were significant delays in the time to the primary outcome for the patients treated with selegiline (median time, 655 days; $P = 0.012$), alpha-tocopherol (670 days, $P = 0.001$) or combination therapy (585 days, $P = 0.049$), as compared with the placebo group (440 days). **CONCLUSIONS:** In patients with moderately severe impairment from Alzheimer's disease, treatment with selegiline or alpha-tocopherol slows the progression of disease.

Calcium carbonate and the premenstrual syndrome: effects on premenstrual and menstrual symptoms. Premenstrual Syndrome Study Group.

Thys-Jacobs S, Starkey P, Bernstein D, Tian J. 1998.
Am J Obstet Gynecol 179(2):444-52

OBJECTIVE: Previous reports have suggested that disturbances in calcium regulation may underlie the pathophysiologic characteristics of premenstrual syndrome and that calcium supplementation may be an effective therapeutic approach. To evaluate the effect of calcium carbonate on the luteal and menstrual phases of the menstrual cycle in premenstrual syndrome, a prospective, randomized, double-blind, placebo-controlled, parallel-group, multicenter clinical trial was conducted. **STUDY DESIGN:** Healthy, premenopausal women between the ages of 18 and 45 years were recruited nationally across the United States at 12 outpatient centers and screened for moderate-to-severe, cyclically recurring premenstrual symptoms. Symptoms were prospectively documented over 2 menstrual cycles with a daily rating scale that had 17 core symptoms and 4 symptom factors (negative affect, water retention, food cravings, and pain). Participants were randomly assigned to receive 1200 mg of elemental calcium per day in the form of calcium carbonate or placebo for 3 menstrual cycles. Routine chemistry, complete blood cell count, and urinalysis were obtained on all participants. Daily documentation of symptoms, adverse effects, and compliance with medications were monitored. The primary outcome measure was the 17-parameter symptom complex score. **RESULTS:** Seven hundred twenty women were screened for this trial; 497 women were enrolled; 466 were valid for the efficacy analysis. There was no difference in age, weight, height, use of oral contraceptives, or menstrual cycle length between treatment groups. There were no differences between groups in the mean screening symptom complex score of the luteal ($P = .659$), menstrual ($P = .818$), or intermenstrual phase ($P = .726$) of the menstrual cycle. During the luteal phase of the treatment cycle, a significantly lower mean symptom complex score was observed in the calcium-treated group for both the second ($P = .007$) and third ($P < .001$) treatment cycles. By the third treatment cycle calcium effectively resulted in an overall 48% reduction in total symptom scores from baseline compared with a 30% reduction in placebo. All 4 symptom factors were significantly reduced by the third treatment cycle. **CONCLUSIONS:** Calcium supplementation is a simple and effective treatment in premenstrual syndrome, resulting in a major reduction in overall luteal phase symptoms.