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## PEER REVIEWED STUDIES

### BLOOD SUGAR BALANCE

#### Fruit and vegetable intake and incidence of type 2 diabetes mellitus: systematic review and meta-analysis

##### ABSTRACT

##### OBJECTIVE:

To investigate the independent effects of intake of fruit and vegetables on incidence of type 2 diabetes.

##### DESIGN:

Systematic review and meta-analysis.

##### DATA SOURCES:

Medline, Embase, CINAHL, British Nursing Index (BNI), and the Cochrane library were searched for medical subject headings and keywords on diabetes, prediabetes, fruit, and vegetables. Expert opinions were sought and reference lists of relevant articles checked.

##### STUDY SELECTION:

Prospective cohort studies with an independent measure of intake of fruit, vegetables, or fruit and vegetables and data on incidence of type 2 diabetes.

##### RESULTS:

Six studies met the inclusion criteria; four of these studies also provided separate information on the consumption of green leafy vegetables. Summary estimates showed that greater intake of green leafy vegetables was associated with a 14% (hazard ratio 0.86, 95% confidence interval 0.77 to 0.97) reduction in risk of type 2 diabetes ( $P=0.01$ ). The summary estimates showed no significant benefits of increasing the consumption of vegetables, fruit, or fruit and vegetables combined.

##### CONCLUSION:

Increasing daily intake of green leafy vegetables could significantly reduce the risk of type 2 diabetes and should be investigated further.

##### Source

Carter P, et al. Fruit and vegetable intake and incidence of type 2 diabetes mellitus: systematic review and meta-analysis. *BMJ*. 2010 Aug 18;341:c4229. doi: 10.1136/bmj.c4229.

### Magnesium intake and risk of type 2 diabetes: a meta-analysis

##### ABSTRACT

##### OBJECTIVE:

To assess the association between magnesium intake and risk of type 2 diabetes.

##### DESIGN:

Meta-analysis of prospective cohort studies.

##### DATA SOURCES:

We retrieved studies published in any language by systematically searching MEDLINE from 1966 to February 2007 and by manually examining the references of the original articles.

##### STUDY SELECTION:

We included prospective cohort studies reporting relative risks with 95% confidence intervals for the association between magnesium intake and incidence of type 2 diabetes.

##### RESULTS:

The seven identified cohort studies of magnesium intake [from foods only ( $n = 4$ ) or from foods and supplements combined ( $n = 3$ )] and incidence of type 2 diabetes included 286,668 participants and 10,912 cases. All but one study found an inverse relation between magnesium intake and risk of type 2 diabetes, and in four studies the association was statistically significant. The overall relative risk for a 100 mg day<sup>-1</sup> increase in magnesium intake was 0.85 (95% CI, 0.79-0.92). Results were similar for intake of dietary magnesium (RR, 0.86; 95% CI, 0.77-0.95) and total magnesium (RR, 0.83; 95% CI, 0.77-0.89). There was no evidence of publication bias ( $P = 0.99$ ).

##### CONCLUSIONS:

Magnesium intake was inversely associated with incidence of type 2 diabetes. This finding suggests that increased consumption of magnesium-rich foods such as whole grains, beans, nuts, and green leafy vegetables may reduce the risk of type 2 diabetes.

##### Source

Larsson SC, Wolk A. Magnesium intake and risk of type 2 diabetes: a meta-analysis. *J Intern Med*. 2007 Aug;262(2):208-14.

### Effects of vitamin D and calcium supplementation on pancreatic B cell function, insulin sensitivity, and glycemia in adults at high risk of diabetes: the Calcium and Vitamin D for Diabetes Mellitus (CaDDM) randomized controlled trial

##### ABSTRACT

##### BACKGROUND:

A suboptimal vitamin D and calcium status has been associated with higher risk of type 2 diabetes in observational studies, but evidence from trials is lacking.

##### OBJECTIVE:

We determined whether vitamin D supplementation, with or without calcium, improved glucose homeostasis in adults at high risk of diabetes.

##### DESIGN:

Ninety-two adults were randomly assigned in a 2-by-2 factorial-design, double-masked, placebo-controlled trial to receive either cholecalciferol (2000 IU once daily) or calcium carbonate (400 mg twice daily) for 16 wk. The primary outcome was the change in pancreatic  $\beta$  cell function as measured by the disposition index after an intravenous-glucose-tolerance test. Other outcomes were acute insulin response, insulin sensitivity, and measures of glycemia.

##### RESULTS:

Participants had a mean age of 57 y, a body mass index (BMI; in kg/m<sup>2</sup>) of 32, and glycated hemoglobin (Hb A(1c)) of 5.9%. There was no significant vitamin D  $\times$  calcium interaction on any outcomes. The disposition index increased in the vitamin D group and decreased in the no-vitamin D group (adjusted mean change  $\pm$  SE:  $300 \pm 130$  compared with  $-126 \pm 127$ , respectively;  $P = 0.011$ ), which was explained by an improvement in insulin secretion ( $62 \pm 39$  compared with  $-36 \pm 37$  mU  $\cdot$  L<sup>-1</sup>  $\cdot$  min, respectively;  $P = 0.046$ ). Hb A(1c) increased less, but nonsignificantly, in the vitamin D group than in the no-vitamin D group ( $0.06 \pm 0.03\%$  compared with  $0.14 \pm 0.03\%$ , respectively;  $P = 0.081$ ). There was no significant difference in any outcomes

with calcium compared with no calcium.

#### CONCLUSION:

In adults at risk of type 2 diabetes, short-term supplementation with cholecalciferol improved  $\beta$  cell function and had a marginal effect on attenuating the rise in Hb A(1c). This trial was registered at clinicaltrials.gov as NCT00436475.

#### Source

Mitri J et al. Effects of vitamin D and calcium supplementation on pancreatic B cell function, insulin sensitivity, and glycemia in adults at high risk of diabetes: the Calcium and Vitamin D for Diabetes Mellitus (CaDDM) randomized controlled trial. Am J

### Influence of magnesium status and magnesium intake on the blood glucose control in patients with type 2 diabetes

#### ABSTRACT

##### Background & Aims

This study was undertaken to assess magnesium intake and magnesium status in patients with type 2 diabetes, and to identify the parameters that best predict alterations in fasting glucose and plasma magnesium.

#### METHODS:

A cross-sectional study was carried out in patients with type 2 diabetes ( $n = 51$ ;  $53.6 \pm 10.5$  y) selected within the inclusion factors, at the University Hospital Onofre Lopes. Magnesium intake was assessed by three 24-h recalls. Urine, plasma and erythrocytes magnesium, fasting and 2-h postprandial glucose, HbA1, microalbuminuria, proteinuria, and serum and urine creatinine were measured.

#### RESULTS:

Mean magnesium intake ( $9.37 \pm 1.76$  mmol/d), urine magnesium ( $2.80 \pm 1.51$  mmol/d), plasma magnesium ( $0.71 \pm 0.08$  mmol/L) and erythrocyte magnesium ( $1.92 \pm 0.23$  mmol/L) levels were low. Seventy-seven percent of participants presented one or more magnesium status parameters below the cut-off points of 3.00 mmol/L for urine, 0.75 mmol/L for plasma and 1.65 mmol/L for erythrocytes. Subjects presented poor blood glucose control with

fasting glucose of  $8.1 \pm 3.7$  mmol/L, 2-h postprandial glucose of  $11.1 \pm 5.1$  mmol/L, and HbA1 of  $11.4 \pm 3.0\%$ . The parameters that influenced fasting glucose were urine, plasma and dietary magnesium, while plasma magnesium was influenced by creatinine clearance.

#### CONCLUSIONS:

Magnesium status was influenced by kidney depuration and was altered in patients with type 2 diabetes, and magnesium showed to play an important role in blood glucose control.

#### Source

Sales CH, et al. Influence of magnesium status and magnesium intake on the blood glucose control in patients with type 2 diabetes. Clin Nutr. 2011 Jan 31. [Epub ahead of print]

### Hypomagnesemia and diabetes mellitus. A review of clinical implications

#### ABSTRACT

Hypomagnesemia has long been known to be associated with diabetes mellitus. Mather et al confirmed the presence of hypomagnesemia in nearly 25% of their diabetic out-patients. Low serum magnesium level has been reported in children with insulin-dependent diabetes and through the entire spectrum of adult type I and type II diabetics regardless of the type of therapy. Hypomagnesemia has been correlated with both poor diabetic control and insulin resistance in nondiabetic elderly patients.

#### Source

Tosiello L, et al. Hypomagnesemia and diabetes mellitus. A review of clinical implications. Arch Intern Med 1996;156:1143-8.

### BONE AND JOINT HEALTH

### Patient level pooled analysis of 68 500 patients from seven major vitamin D fracture trials in US and Europe

#### ABSTRACT

#### OBJECTIVES:

To identify participants' characteristics that influence the anti-fracture efficacy of vitamin D or vitamin D plus calcium with respect to any fracture, hip fracture, and clinical vertebral fracture and to assess the influence of dosing regimens and co-administration of calcium.

#### DESIGN:

Individual patient data analysis using pooled data from randomised trials.

#### Data sources

Seven major randomised trials of vitamin D with calcium or vitamin D alone, yielding a total of 68 517 participants (mean age 69.9 years, range 47-107 years, 14.7% men).

#### STUDY SELECTION:

Studies included were randomised studies with at least one intervention arm in which vitamin D was given, fracture as an outcome, and at least 1000 participants.

#### DATA SYNTHESIS:

Logistic regression analysis was used to identify significant interaction terms, followed by Cox's proportional hazards models incorporating age, sex, fracture history, and hormone therapy and bisphosphonate use.

#### RESULTS:

Trials using vitamin D with calcium showed a reduced overall risk of fracture (hazard ratio 0.92, 95% confidence interval 0.86 to 0.99,  $P=0.025$ ) and hip fracture (all studies: 0.84, 0.70 to 1.01,  $P=0.07$ ; studies using 10  $\mu$ g of vitamin D given with calcium: 0.74, 0.60 to 0.91,  $P=0.005$ ). For vitamin D alone in daily doses of 10  $\mu$ g or 20  $\mu$ g, no significant effects were found. No interaction was found between fracture history and treatment response, nor any interaction with age, sex, or hormone replacement therapy.

#### CONCLUSION:

This individual patient data analysis indicates that vitamin D given alone in doses of 10-20  $\mu$ g is not effective in preventing fractures. By contrast, calcium and vitamin D given together reduce hip fractures and total fractures, and probably

vertebral fractures, irrespective of age, sex, or previous fractures.

#### Source

Abrahamsen B, et al. Patient level pooled analysis of 68 500 patients from seven major vitamin D fracture trials in US and Europe. DIPART (Vitamin D Individual Patient Analysis of Randomized Trials) Group. BMJ. 2010 Jan 12;340:b5463.

### **A Multi-nutrient supplement reduced markers of inflammation and improved physical performance in active individuals of middle to older age: a randomized, double-blind, placebo-controlled study**

#### ABSTRACT

##### **BACKGROUND:**

While exercise acts to combat inflammation and aging, the ability to exercise may itself be compromised by inflammation and inflammation's impact on muscle recovery and joint inflammation. A number of nutritional supplements have been shown to reduce inflammation and improve recovery. The purpose of the current investigation was to examine the effect of a multi-nutrient supplement containing branched chain amino acids, taurine, anti-inflammatory plant extracts, and B vitamins on inflammatory status, endothelial function, physical function, and mood in middle-aged individuals.

##### **METHODS:**

Thirty-one healthy and active men (N = 16, mean age  $56 \pm 6.0$  yrs) and women (N = 15, mean age =  $52 \pm 7.5$  yrs) participated in this investigation. Subjects completed one 28 day cycle of placebo supplementation and one 28 day cycle of multi-nutrient supplementation (separated by a one week washout period) in a balanced, randomized, double-blind, cross-over design. Subjects completed weekly perceptual logs (PROMIS-57, KOOS) and pre- and post-testing around the supplementation period. Testing consisted of brachial artery flow mediated dilation (FMD), blood measures, and physical performance on vertical jump, handgrip strength, and balance (dispersion from center of pressure). Significance for

the investigation was  $p \leq 0.05$ .

##### **Results**

IL-6 significantly decreased in both men (from  $1.2 \pm 0.2$  to  $0.7 \pm 0.4$  pg-mL<sup>-1</sup>) and women (from  $1.16 \pm 0.04$  to  $0.7 \pm 0.4$  pg-mL<sup>-1</sup>). Perceived energy also improved for both men (placebo:  $1.8 \pm 0.7$ ; supplement:  $3.7 \pm 0.8$  AUC) and women (placebo:  $1.2 \pm 0.7$ ; supplement:  $2.8 \pm 0.8$  AUC). Alpha-1-antichymotrypsin (from  $108.9 \pm 38.6$  to  $55.5 \pm 22.2$  ug-mL<sup>-1</sup>), Creatine Kinase (from  $96 \pm 34$  to  $67 \pm 23$  IU-L<sup>-1</sup>), general pain, and joint pain decreased in men only, while anxiety and balance (from  $0.52 \pm 0.13$  to  $0.45 \pm 0.12$  cm) improved in women only. Men showed increased performance in vertical jump power (from  $2642 \pm 244$  to  $3134 \pm 282$  W) and grip strength (from  $42.1 \pm 5.9$  to  $48.5 \pm 4.9$  kg).

##### **CONCLUSIONS:**

A multi-nutrient supplement is effective in improving inflammatory status in both men and women, markers of pain, joint pain, strength, and power in men only, and both anxiety and balance (a risk factor for hip fracture) in women. Therefore, a multi-nutrient supplement may help middle-aged individuals to prolong physical function and maintain a healthy, active lifestyle.

#### Source

Dunn-Lewis C et al. A Multi-nutrient supplement reduced markers of inflammation and improved physical performance in active individuals of middle to older age: a randomized, double-blind, placebo-controlled study. Nutr J 10:90, 2011.

### **Calcium and vitamin-D supplementation on bone structural properties in peripubertal female identical twins: a randomized controlled trial**

#### ABSTRACT

A randomised controlled trial was used in assessing the impact of 6 months of daily calcium and vitamin-D supplementation on trabecular and cortical bone acquisition at distal tibial and radial sites using peripheral quantitative computed tomography (pQCT). Daily supplementation was associated with increased bone density and bone strength

at the distal tibia and radius.

##### **INTRODUCTION:**

pQCT has not been used to assess bone responses to calcium and vitamin-D supplementation on peripubertal children. This randomised controlled trial aimed to assess the impact of a 6-month daily calcium and vitamin-D supplementation on trabecular and cortical bone acquisition at distal tibial and radial sites using pQCT.

##### **METHODS:**

Twenty pairs of peripubertal female identical twins, aged 9 to 13 years, were randomly assigned to receive either 800 mg of calcium and 400 IU of vitamin D<sub>3</sub>, or a matched placebo. Bone structural properties at the distal tibia and distal radius were acquired at baseline and 6 months.

##### **RESULTS:**

The calcium-supplemented group showed greater gains in trabecular density, trabecular area and strength strain index at the 4% of distal tibial and radial sites compared with the placebo group ( $p=0.001$ ). Greater gains in cortical area at the 38% and 66% of tibial sites were also found in twins receiving the calcium supplement ( $p=0.001$ ).

##### **CONCLUSIONS:**

Daily supplementation for a period of 6 months was associated with increased trabecular area, trabecular density and strength strain index at the ultra-distal tibia and radius and increased cortical area at tibial mid-shaft.

#### Source

Greene DA, et al. Calcium and vitamin-D supplementation on bone structural properties in peripubertal female identical twins: a randomized controlled trial. osteoporos Int. 2011 Feb;22(2):489-98. Epub 2010 Jun 11.

### **Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease**

#### ABSTRACT

Most humans depend on sun exposure

to satisfy their requirements for vitamin D. Solar ultraviolet B photons are absorbed by 7-dehydrocholesterol in the skin, leading to its transformation to previtamin D3, which is rapidly converted to vitamin D3. Season, latitude, time of day, skin pigmentation, aging, sunscreen use, and glass all influence the cutaneous production of vitamin D3. Once formed, vitamin D3 is metabolized in the liver to 25-hydroxyvitamin D3 and then in the kidney to its biologically active form, 1,25-dihydroxyvitamin D3. Vitamin D deficiency is an unrecognized epidemic among both children and adults in the United States. Vitamin D deficiency not only causes rickets among children but also precipitates and exacerbates osteoporosis among adults and causes the painful bone disease osteomalacia. Vitamin D deficiency has been associated with increased risks of deadly cancers, cardiovascular disease, multiple sclerosis, rheumatoid arthritis, and type 1 diabetes mellitus. Maintaining blood concentrations of 25-hydroxyvitamin D above 80 nmol/L (approximately 30 ng/mL) not only is important for maximizing intestinal calcium absorption but also may be important for providing the extrarenal 1 $\alpha$ -hydroxylase that is present in most tissues to produce 1,25-dihydroxyvitamin D3. Although chronic excessive exposure to sunlight increases the risk of nonmelanoma skin cancer, the avoidance of all direct sun exposure increases the risk of vitamin D deficiency, which can have serious consequences. Monitoring serum 25-hydroxyvitamin D concentrations yearly should help reveal vitamin D deficiencies. Sensible sun exposure (usually 5-10 min of exposure of the arms and legs or the hands, arms, and face, 2 or 3 times per week) and increased dietary and supplemental vitamin D intakes are reasonable approaches to guarantee vitamin D sufficiency.

Source

Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *Am J Clin Nutr.* 2004 Dec;80(6 Suppl):1678S-88S.

**Effects of vitamin D and calcium supplementation on pancreatic B cell function, insulin sensitivity, and glycemia in adults at high risk of diabetes: the Calcium and Vitamin D for Diabetes Mellitus (CaDDM) randomized controlled trial**

**ABSTRACT**

**BACKGROUND:**

A suboptimal vitamin D and calcium status has been associated with higher risk of type 2 diabetes in observational studies, but evidence from trials is lacking.

**OBJECTIVE:**

We determined whether vitamin D supplementation, with or without calcium, improved glucose homeostasis in adults at high risk of diabetes.

**DESIGN:**

Ninety-two adults were randomly assigned in a 2-by-2 factorial-design, double-masked, placebo-controlled trial to receive either cholecalciferol (2000 IU once daily) or calcium carbonate (400 mg twice daily) for 16 wk. The primary outcome was the change in pancreatic  $\beta$  cell function as measured by the disposition index after an intravenous-glucose-tolerance test. Other outcomes were acute insulin response, insulin sensitivity, and measures of glycemia.

**RESULTS:**

Participants had a mean age of 57 y, a body mass index (BMI; in kg/m<sup>2</sup>) of 32, and glycated hemoglobin (Hb A(1c)) of 5.9%. There was no significant vitamin D  $\times$  calcium interaction on any outcomes. The disposition index increased in the vitamin D group and decreased in the no-vitamin D group (adjusted mean change  $\pm$  SE: 300  $\pm$  130 compared with -126  $\pm$  127, respectively;  $P$  = 0.011), which was explained by an improvement in insulin secretion (62  $\pm$  39 compared with -36  $\pm$  37 mU  $\cdot$  L(-1)  $\cdot$  min, respectively;  $P$  = 0.046). Hb A(1c) increased less, but nonsignificantly, in the vitamin D group than in the no-vitamin D group (0.06  $\pm$  0.03% compared with 0.14  $\pm$  0.03%, respectively;  $P$  = 0.081). There was no significant difference in any outcomes with calcium compared with no

calcium.

**CONCLUSION:**

In adults at risk of type 2 diabetes, short-term supplementation with cholecalciferol improved  $\beta$  cell function and had a marginal effect on attenuating the rise in Hb A(1c). This trial was registered at clinicaltrials.gov as NCT00436475.

Source

Mitri J et al. Effects of vitamin D and calcium supplementation on pancreatic B cell function, insulin sensitivity, and glycemia in adults at high risk of diabetes: the Calcium and Vitamin D for Diabetes Mellitus (CaDDM) randomized controlled trial. *Am J*

**Magnesium intake from food and supplements is associated with bone mineral density in healthy older white subjects**

**ABSTRACT**

**OBJECTIVES:**

To determine whether magnesium intake from supplemental and dietary sources is associated with bone mineral density (BMD) in older men and women.

**DESIGN:**

Cross-sectional.

**SETTING:**

Memphis, Tennessee, and Pittsburgh, Pennsylvania.

**PARTICIPANTS:**

Two thousand thirty-eight older black and white men and women aged 70 to 79 at baseline enrolled in the Health, Aging and Body Composition Study.

**MEASUREMENTS:**

Dietary intake of magnesium was assessed using a semiquantitative food frequency questionnaire, and supplement data were collected based on a medication inventory. BMD of the whole body was obtained using a fan-beam densitometer. Additional covariates included age, body mass index (BMI), smoking status, alcohol use, physical activity, estrogen use, and supplemental calcium (Ca) and vitamin D use.

**RESULTS:**

In white, but not black, men and



women, magnesium intake was positively associated with BMD of the whole body after adjustment for age, self-report of osteoporosis or fracture in adulthood, caloric intake, Ca and vitamin D intake, BMI, smoking status, alcohol intake, physical activity, thiazide diuretic use, and estrogen use in women ( $P=.05$  for men and  $P=.005$  for women). BMD was  $0.04 \text{ g/cm}^2$  higher in white women and  $0.02 \text{ g/cm}^2$  higher in white men in the highest than in the lowest quintile of magnesium intake.

#### CONCLUSION:

Greater magnesium intake was significantly related to higher BMD in white women and men. The lack of association observed in black women and men may be related to differences in Ca regulation or in nutrient reporting.

#### Source

Ryder KM, et al. Magnesium intake from food and supplements is associated with bone mineral density in healthy older white subjects. *J Am Geriatr Soc.* 2005 Nov;53(11):1875-80.

#### Calcium and vitamin D supplementation through fortified dairy products counterbalances seasonal variations of bone metabolism indices: the Postmenopausal Health Study

#### ABSTRACT

##### PURPOSE:

To assess the effectiveness of a dietary intervention combined with fortified dairy products on bone metabolism and bone mass indices in postmenopausal women.

##### METHODS:

Forty postmenopausal women (55-65 years old) were equally randomized into a dietary group (DG), receiving daily and for 30 months, 1,200 mg of calcium and  $7.5 \mu\text{g}$  of vitamin D(3) for the first 12 months that increased to  $22.5 \mu\text{g}$  for the remaining 18 months of intervention through fortified dairy products; and a control group (CG). Differences in the changes of bone metabolism and bone mass indices were examined with repeated measures ANOVA.

##### RESULTS:

A significant increase was observed for

PTH levels only in the CG during the first six winter months of intervention ( $p = 0.049$ ). After 30 months of intervention, during winter, serum 25(OH)D significantly decreased in the CG while remained in the same high levels as in the summer period in the DG. Serum RANKL levels decreased significantly in the DG compared with the increase in the CG during the 30-month intervention period ( $p = 0.005$ ). Serum CTx decreased significantly in the DG after six (-0.08; -0.12 to -0.03) and 12 (-0.03; -0.08 to -0.02) months of intervention. Finally, the DG had more favorable changes in total body BMD than the CG ( $p < 0.001$ ).

#### CONCLUSIONS:

Increasing dietary intake of calcium and vitamin D in osteopenic postmenopausal women appears to be effective in producing favorable changes in several bone metabolism and bone mass indices and in counterbalancing seasonal variations in hormonal and biochemical molecules.

#### Source

Tenta R, et al. Calcium and vitamin D supplementation through fortified dairy products counterbalances seasonal variations of bone metabolism indices: the Postmenopausal Health Study. *Eur J Nutr.* 2010 Dec 14. [Epub ahead of print]

#### BREAST HEALTH

#### The role of vitamin D in cancer prevention

#### ABSTRACT

Vitamin D status differs by latitude and race, with residents of the northeastern United States and individuals with more skin pigmentation being at increased risk of deficiency. A PubMed database search yielded 63 observational studies of vitamin D status in relation to cancer risk, including 30 of colon, 13 of breast, 26 of prostate, and 7 of ovarian cancer, and several that assessed the association of vitamin D receptor genotype with cancer risk. The majority of studies found a protective relationship between sufficient vitamin

D status and lower risk of cancer. The evidence suggests that efforts to improve vitamin D status, for example by vitamin D supplementation, could reduce cancer incidence and mortality at low cost, with few or no adverse effects.

#### Source

Garland CF, et al. The role of vitamin D in cancer prevention. *Am J Public Health.* 2006 Feb;96(2):252-61.

#### CELLULAR HEALTH

#### Protective role of 1 alpha, 25-dihydroxyvitamin D3 against oxidative stress in nonmalignant human prostate epithelial cells

#### ABSTRACT

Overproduction of reactive oxygen species (ROS), through either endogenous or exogenous sources, could induce DNA damage, and accumulation of DNA damage might lead to multistep carcinogenesis. The antioxidative effects of vitamin D have been suggested by epidemiological and many in vitro and in vivo laboratory studies. While exploring the antioxidative effects of vitamin D in prostate cells, we found that the active form of vitamin D, 1 alpha, 25-dihydroxyvitamin D(3) (1,25-VD), can protect nonmalignant human prostate epithelial cell lines, BPH-1 and RWPE-1, but not malignant human prostate epithelial cells, CWR22R and DU 145, from oxidative stress-induced cell death. Glucose-6-phosphate dehydrogenase (G6PD), a key antioxidant enzyme, was dose- and time-dependently induced by 1,25-VD. Mechanistic studies using chromatin immunoprecipitation (ChIP) assay revealed that a direct repeat-3 (DR3) vitamin D response element located in the first intron of the G6PD genome can be bound by liganded vitamin D receptor, thereby regulating G6PD gene expression. Increasing G6PD activity and glutathione level by 1,25-VD can scavenge cellular ROS. Moreover, the protective effects of 1,25-VD were

abolished by dehydroepiandrosterone, a noncompetitive inhibitor of G6PD activity. Together, our results showed that 1,25-VD can protect nonmalignant prostate cells from oxidative stress-induced cell death by elimination of ROS-induced cellular injuries through transcriptional activation of G6PD activity. The antioxidative effect of vitamin D strengthens its roles in cancer chemoprevention and adds to a growing list of beneficial effects of vitamin D against cancer.

#### Source

Bao BY, et al. Protective role of 1 alpha, 25-dihydroxyvitamin D3 against oxidative stress in nonmalignant human prostate epithelial cells. *Int J Cancer*. 2008 Jun 15;122(12):2699-706

### Cognitive and clinical outcomes of homocysteine-lowering B-vitamin treatment in mild cognitive impairment: a randomized controlled trial

#### Abstract

##### BACKGROUND:

Homocysteine is a risk factor for Alzheimer's disease. In the first report on the VITACOG trial, we showed that homocysteine-lowering treatment with B vitamins slows the rate of brain atrophy in mild cognitive impairment (MCI). Here we report the effect of B vitamins on cognitive and clinical decline (secondary outcomes) in the same study.

##### METHODS:

This was a double-blind, single-centre study, which included participants with MCI, aged  $\geq 70$  y, randomly assigned to receive a daily dose of 0.8 mg folic acid, 0.5 mg vitamin B(12) and 20 mg vitamin B(6) (133 participants) or placebo (133 participants) for 2 y. Changes in cognitive or clinical function were analysed by generalized linear models or mixed-effects models.

##### RESULTS:

The mean plasma total homocysteine was 30% lower in those treated with B vitamins relative to placebo. B vitamins stabilized executive function (CLOX) relative to placebo ( $P = 0.015$ ). There was significant

benefit of B-vitamin treatment among participants with baseline homocysteine above the median (11.3  $\mu\text{mol/L}$ ) in global cognition (Mini Mental State Examination,  $P < 0.001$ ), episodic memory (Hopkins Verbal Learning Test-delayed recall,  $P = 0.001$ ) and semantic memory (category fluency,  $P = 0.037$ ). Clinical benefit occurred in the B-vitamin group for those in the upper quartile of homocysteine at baseline in global clinical dementia rating score ( $P = 0.02$ ) and IQCODE score ( $P = 0.01$ ).

##### CONCLUSION:

In this small intervention trial, B vitamins appear to slow cognitive and clinical decline in people with MCI, in particular in those with elevated homocysteine. Further trials are needed to see if this treatment will slow or prevent conversion from MCI to dementia.

#### Source

de Jager CA et al. Cognitive and clinical outcomes of homocysteine-lowering B-vitamin treatment in mild cognitive impairment: a randomized controlled trial. *Int J Geriatr Psychiatry* [Epub ahead of print, July, 2011]

### Physicians and nurses use and recommend dietary supplements: report of a survey

#### ABSTRACT

##### BACKGROUND:

Homocysteine is a risk factor for Alzheimer's disease. In the first report on the VITACOG trial, we showed that homocysteine-lowering treatment with B vitamins slows the rate of brain atrophy in mild cognitive impairment (MCI). Here we report the effect of B vitamins on cognitive and clinical decline (secondary outcomes) in the same study.

##### METHODS:

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by generalized linear models or mixed-effects models.

##### RESULTS:

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##### CONCLUSION:

In this small intervention trial, B vitamins appear to slow cognitive and clinical decline in people with MCI, in particular in those with elevated homocysteine. Further trials are needed to see if this treatment will slow or prevent conversion from MCI to dementia.

#### Source

Dickinson A, et al. Physicians and nurses use and recommend dietary supplements: report of a survey. *Nutr J*. 2009 Jul 1;8:29.

### Effects of a carotene-deficient diet on measures of oxidative susceptibility and superoxide dismutase activity in adult women

#### ABSTRACT

The effect of consuming a low carotene diet (approximately 60 micrograms carotene/day) on oxidative susceptibility and superoxide dismutase (SOD) activity in women living in a metabolic research unit was evaluated. The diet had sufficient vitamins A, E, and C. The women ate the diet supplemented with 1500 micrograms/day beta-carotene for 4 days (baseline), then the unsupplemented diet for 68 days (depletion), followed

by the diet supplemented with > 15,000 micrograms/day carotene for 28 days (repletion). Production of hexanal, pentanal, and pentane by copper-oxidized plasma low density lipoproteins from carotene-depleted women was greater than their production of these compounds when repleted with carotene. Erythrocyte SOD activity was depressed in carotene-depleted women; it recovered with repletion. Thiobarbituric acid reactive substances in plasma of carotene-depleted women were elevated and diminished with repletion. Dietary carotene seems to be needed, not only as a precursor of vitamin A, but also to inhibit oxidative damage and decrease oxidation susceptibility.

#### Source

Dixon ZR, et al. Effects of a carotene-deficient diet on measures of oxidative susceptibility and superoxide dismutase activity in adult women. *Free Radic Biol Med.* 1994 Dec;17(6):537-44.

#### Effect of low carotene diet on malondialdehyde (MDA) concentration

**\*Note: This study does not apply to Formula IV.**

#### ABSTRACT

##### OBJECTIVE:

The purpose of the study was to evaluate the effect of a low carotenoid diet (83 micrograms Beta-carotene) on malondialdehyde-thiobarbituric acid (MDA-TBA) concentrations of nine premenopausal women.

##### METHODS:

Subjects lived on the metabolic research unit of the Western Human Nutrition Research Center (WHNRC), where diet, exercise and other activities were controlled. Five subjects (Group C, control group) consumed a low carotenoid diet and received an additional 0.5 mg/day of Beta-carotene while four subjects (Group P, placebo group) received only the low carotenoid diet during days 1 to 60 (period 1). All subjects received 0.5 mg/day of Beta-carotene during days 60 to 100 (period 2), plus three capsules/day mixed carotenoid supplement (Neo-Life Company)

during study days 100 to 120. Changes in MDA-TBA concentrations were analyzed during the study periods and between the groups.

##### RESULTS:

At the start of the study (day 1), no significant difference in the MDA-TBA concentration was observed between the control (Group C) and the placebo (Group P) subjects. During period 1 (days 2 to 60), when Group P subjects consumed the low carotenoid diet without supplementation, the MDA-TBA values for Group P rose markedly and were significantly ( $p < 0.05$ ) higher than the MDA-TBA values for Group C subjects who were receiving carotenoid supplementation. During period 2 (days 60 to 100) when both groups received carotenoid supplementation, the MDA-TBA values of Group P subjects were significantly ( $p < 0.05$ ) reduced to the point where they were similar to the MDA-TBA values for Group C subjects.

##### CONCLUSIONS:

These findings provide evidence to support the beneficial effects of carotenoids in preventing lipid peroxidation in the cells. Further studies are needed to identify the exact mechanism by which carotenoids prevent lipid peroxidation and the amount needed for normal activity.

#### Source

Dixon ZR, et al. Effect of low carotene diet on malondialdehyde (MDA) concentration; *Free Radic Biol Med.* 1996.

#### Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease

#### ABSTRACT

Most humans depend on sun exposure to satisfy their requirements for vitamin D. Solar ultraviolet B photons are absorbed by 7-dehydrocholesterol in the skin, leading to its transformation to previtamin D3, which is rapidly converted to vitamin D3. Season, latitude, time of day, skin pigmentation, aging, sunscreen use, and glass all influence the cutaneous production of vitamin D3. Once formed, vitamin D3 is metabolized in the liver to

25-hydroxyvitamin D3 and then in the kidney to its biologically active form, 1,25-dihydroxyvitamin D3. Vitamin D deficiency is an unrecognized epidemic among both children and adults in the United States. Vitamin D deficiency not only causes rickets among children but also precipitates and exacerbates osteoporosis among adults and causes the painful bone disease osteomalacia. Vitamin D deficiency has been associated with increased risks of deadly cancers, cardiovascular disease, multiple sclerosis, rheumatoid arthritis, and type 1 diabetes mellitus. Maintaining blood concentrations of 25-hydroxyvitamin D above 80 nmol/L (approximately 30 ng/mL) not only is important for maximizing intestinal calcium absorption but also may be important for providing the extrarenal 1 $\alpha$ -hydroxylase that is present in most tissues to produce 1,25-dihydroxyvitamin D3. Although chronic excessive exposure to sunlight increases the risk of nonmelanoma skin cancer, the avoidance of all direct sun exposure increases the risk of vitamin D deficiency, which can have serious consequences. Monitoring serum 25-hydroxyvitamin D concentrations yearly should help reveal vitamin D deficiencies. Sensible sun exposure (usually 5-10 min of exposure of the arms and legs or the hands, arms, and face, 2 or 3 times per week) and increased dietary and supplemental vitamin D intakes are reasonable approaches to guarantee vitamin D sufficiency.

#### Source

Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *Am J Clin Nutr.* 2004 Dec;80(6 Suppl):1678S-88S.

#### Effects of vitamin D and calcium supplementation on pancreatic B cell function, insulin sensitivity, and glycemia in adults at high risk of diabetes: the Calcium and Vitamin D for Diabetes Mellitus (CaDDM) randomized controlled trial



## ABSTRACT

### BACKGROUND:

A suboptimal vitamin D and calcium status has been associated with higher risk of type 2 diabetes in observational studies, but evidence from trials is lacking.

### OBJECTIVE:

We determined whether vitamin D supplementation, with or without calcium, improved glucose homeostasis in adults at high risk of diabetes.

### DESIGN:

Ninety-two adults were randomly assigned in a 2-by-2 factorial-design, double-masked, placebo-controlled trial to receive either cholecalciferol (2000 IU once daily) or calcium carbonate (400 mg twice daily) for 16 wk. The primary outcome was the change in pancreatic  $\beta$  cell function as measured by the disposition index after an intravenous-glucose-tolerance test. Other outcomes were acute insulin response, insulin sensitivity, and measures of glycemia.

### RESULTS:

Participants had a mean age of 57 y, a body mass index (BMI; in kg/m<sup>2</sup>) of 32, and glycated hemoglobin (Hb A(1c)) of 5.9%. There was no significant vitamin D  $\times$  calcium interaction on any outcomes. The disposition index increased in the vitamin D group and decreased in the no-vitamin D group (adjusted mean change  $\pm$  SE: 300  $\pm$  130 compared with -126  $\pm$  127, respectively;  $P = 0.011$ ), which was explained by an improvement in insulin secretion (62  $\pm$  39 compared with -36  $\pm$  37 mU  $\cdot$  L(-1)  $\cdot$  min, respectively;  $P = 0.046$ ). Hb A(1c) increased less, but nonsignificantly, in the vitamin D group than in the no-vitamin D group (0.06  $\pm$  0.03% compared with 0.14  $\pm$  0.03%, respectively;  $P = 0.081$ ). There was no significant difference in any outcomes with calcium compared with no calcium.

### CONCLUSION:

In adults at risk of type 2 diabetes, short-term supplementation with cholecalciferol improved  $\beta$  cell function and had a marginal effect on attenuating the rise in Hb A(1c). This trial was registered at [clinicaltrials.gov](http://clinicaltrials.gov) as NCT00436475.

## Source

Mitri J et al. Effects of vitamin D and calcium supplementation on pancreatic B cell function, insulin sensitivity, and glycemia in adults at high risk of diabetes: the Calcium and Vitamin D for Diabetes Mellitus (CaDDM) randomized controlled trial. *Am J*

### Expression of the multiple sclerosis-associated MHC class II Allele HLA-DRB1\*1501 is regulated by vitamin D

## ABSTRACT

Multiple sclerosis (MS) is a complex trait in which allelic variation in the MHC class II region exerts the single strongest effect on genetic risk. Epidemiological data in MS provide strong evidence that environmental factors act at a population level to influence the unusual geographical distribution of this disease. Growing evidence implicates sunlight or vitamin D as a key environmental factor in aetiology. We hypothesised that this environmental candidate might interact with inherited factors and sought responsive regulatory elements in the MHC class II region. Sequence analysis localised a single MHC vitamin D response element (VDRE) to the promoter region of HLA-DRB1. Sequencing of this promoter in greater than 1,000 chromosomes from HLA-DRB1 homozygotes showed absolute conservation of this putative VDRE on HLA-DRB1\*15 haplotypes. In contrast, there was striking variation among non-MS-associated haplotypes. Electrophoretic mobility shift assays showed specific recruitment of vitamin D receptor to the VDRE in the HLA-DRB1\*15 promoter, confirmed by chromatin immunoprecipitation experiments using lymphoblastoid cells homozygous for HLA-DRB1\*15. Transient transfection using a luciferase reporter assay showed a functional role for this VDRE. B cells transiently transfected with the HLA-DRB1\*15 gene promoter showed increased expression on stimulation with 1,25-dihydroxyvitamin D3 ( $P = 0.002$ ) that was lost both on deletion of the VDRE or with the homologous "VDRE" sequence found in non-MS-associated

HLA-DRB1 haplotypes. Flow cytometric analysis showed a specific increase in the cell surface expression of HLA-DRB1 upon addition of vitamin D only in HLA-DRB1\*15 bearing lymphoblastoid cells. This study further implicates vitamin D as a strong environmental candidate in MS by demonstrating direct functional interaction with the major locus determining genetic susceptibility. These findings support a connection between the main epidemiological and genetic features of this disease with major practical implications for studies of disease mechanism and prevention.

## Source

Ramagopalan SV, et al. Expression of the multiple sclerosis-associated MHC class II Allele HLA-DRB1\*1501 is regulated by vitamin D. *PLoS Genet.* 2009 Feb;5(2):e1000369.

### Low serum 25-hydroxyvitamin D concentrations are associated with greater all-cause mortality in older community-dwelling women

## ABSTRACT

Vitamin D deficiency is associated with osteoporosis, poor muscle strength, falls, and fractures. The relationship between serum vitamin D concentrations and mortality in older community-dwelling women has not been well characterized. We hypothesized that women with lower 25-hydroxyvitamin D (25[OH]D) concentrations were at higher risk of mortality. We examined the association between serum 25[OH]D concentrations and all-cause mortality in a prospective, population-based study of 714 community-dwelling women, aged 70 to 79 years, the Women's Health and Aging Studies I and II in Baltimore, Md. The studies were originally designed to evaluate the causes and course of physical disability in older women living in the community. Vital status was determined through follow-up interviews and matching with the National Death Index. During a median of 72 months of follow-up, 100 (14%) of 714 women died.

Women in the lowest quartile of 25(OH) D (<15.3 ng/mL or 38.2 nmol/L) were at higher risk of death (hazards ratio, 2.45; 95% confidence interval, 1.12-5.36; P = .02) compared to women in the highest quartile (>27.0 ng/mL or 67.4 nmol/L) of 25(OH)D in a multivariate Cox proportional hazards model adjusting for demographics, season, and conventional risk factors. Older community-dwelling women with low 25(OH)D levels are at an increased risk of death.

Source

Semba R, et al. Low serum 25-hydroxyvitamin D concentrations are associated with greater all-cause mortality in older community-dwelling women. *Nutr Resear*. 2009 Aug;29(8):525-30

### Vitamin D and chronic pain

#### ABSTRACT

##### RESULTS:

We identified 22 relevant studies that reported mean 25-OH vitamin D levels and/or investigated the results of vitamin D treatment in patients with chronic pain conditions. Five were randomized double blind trials of vitamin D treatment [12,13,15,23,33]. Eight studies with weaker designs more prone to bias also evaluated vitamin D treatment; two were randomised but not double blind [19,32] and six were case series [2,9,11,14,21,28]. Nine purely observational studies were without treatment [3,4,7,16,18,22,26,27,30]. One study [4] reported results separately for men and women and was treated as two data sets. These 23 data sets ranged in size from 5 to 3459 patients. The total number of patients in “pain” and “control” groups was 8644; 58% were women. Few studies actually measured vitamin D status, and there was no common definition of what constituted deficiency. The expected dependence of 25-OH vitamin D level on latitude was confirmed, with lower average levels at higher latitude, though with considerable variability between populations (Fig. 1). Three observational studies explored differences in 25-OH vitamin D levels

between patients with and without chronic musculoskeletal or widespread pain. Two very small studies (104 patients in total) [7,22] claimed significantly reduced 25-OH vitamin D levels in pain subjects compared with controls. In a large study [4], a significant association between 25-OH vitamin D levels and increased pain was found in only one of the several analyses for 3495 women, but not for 3365 men. Another study [33] investigated 25-OH vitamin D levels in patients with diffuse musculoskeletal pain and used patients with osteoarthritis as a “control” group. It found no difference in 25-OH vitamin D levels between these two populations; because the control group also consisted of patients with a chronically painful condition, both groups of patients from this study are treated as “pain” populations for the purpose of this review.

Characteristics of treatment studies are in Table 1. Vitamin D treatments involved monthly equivalent doses between 1200 and 400,000 IU. Fourteen studies were in musculoskeletal pain [2,7,11–14,16,19,22,23,27,28,32,33], five in chronic widespread pain or fibromyalgia [3,4,9,18,26], one in diabetic subjects with neuropathic pain [21], one addressing an unusual hyperaesthetic pain syndrome [14], and one with various conditions [30]. Patients in these studies may have had ill-defined subclinical or overt osteomalacia, as is not infrequently the case with vitamin D deficiency. Duration of treatment was from a few days to 12 months, though most studies lasted two months or more. It was rare for studies to report on adverse events. Treatment studies involved 733 patients. Randomised double blind trials involved 229 patients, of whom only 22 (10%) were in a trial with a significant improvement in pain with vitamin D, and then only on a pain mobility measure; 207 patients were in trials with no significant improvement in pain with vitamin D. Only one of these randomised trials [33] measured 25-OH vitamin D, demonstrating both deficiency at baseline and significant change with treatment. By contrast, six of eight treatment studies that were not double blind showed significant improvement in pain with vitamin D (457 of

504 patients, 93%). Only three of these trials [9,11,28] measured vitamin status. There was no apparent correlation between significant improvement in pain with vitamin D and a particular preparation, dose, or condition (Table 1).

Source

Straube S, et al. Vitamin D and chronic pain. *Pain*. 2009 Jan;141(1-2):10-3. Epub 2008 Dec 11.

### CHILDREN'S HEALTH

#### High prevalence of vitamin D insufficiency in black and white pregnant women residing in the Northern United States and their neonates

#### ABSTRACT

In utero or early-life vitamin D deficiency is associated with skeletal problems, type 1 diabetes, and schizophrenia, but the prevalence of vitamin D deficiency in U.S. pregnant women is unexplored. We sought to assess vitamin D status of pregnant women and their neonates residing in Pittsburgh by race and season. Serum 25-hydroxyvitamin D (25(OH)D) was measured at 4-21 wk gestation and predelivery in 200 white and 200 black pregnant women and in cord blood of their neonates. Over 90% of women used prenatal vitamins. Women and neonates were classified as vitamin D deficient [25(OH)D<37.5 nmol/L], insufficient [25(OH)D 37.5-80 nmol/L], or sufficient [25(OH)D>80 nmol/L]. At delivery, vitamin D deficiency and insufficiency occurred in 29.2% and 54.1% of black women and 45.6% and 46.8% black neonates, respectively. Five percent and 42.1% of white women and 9.7% and 56.4% of white neonates were vitamin D deficient and insufficient, respectively. Results were similar at <22 wk gestation. After adjustment for prepregnancy BMI and periconceptional multivitamin use, black women had a smaller mean increase in maternal 25(OH)D compared with white women from winter to summer

(16.0+/-3.3 nmol/L vs. 23.2+/-3.7 nmol/L) and from spring to summer (13.2+/-3.0 nmol/L vs. 27.6+/-4.7 nmol/L) ( $P<0.01$ ). These results suggest that black and white pregnant women and neonates residing in the northern US are at high risk of vitamin D insufficiency, even when mothers are compliant with prenatal vitamins. Higher-dose supplementation is needed to improve maternal and neonatal vitamin D nutriture.

#### Source

Bodnar et al. High prevalence of vitamin D insufficiency in black and white pregnant women residing in the Northern United States and their neonates. *J Nutr* 2007;137:447-52.

### Periconceptional multivitamin use and infant birth weight disparities

#### ABSTRACT

##### PURPOSE:

In the United States, African American women deliver preterm and low birth weight infants two to three times more frequently than their white counterparts. Our objective was to determine whether maternal periconceptional multivitamin (MVI) use is associated with this disparity.

##### METHODS:

As a secondary analysis of previously collected data from mothers of non-malformed infants from the Slone Epidemiology Center Birth Defects Study, we conducted a retrospective cohort study of 2331 non-Hispanic white and 133 non-Hispanic black mother/infant pairs from 1998 through 2007. To estimate the effect of MVI use on birth outcomes, linear regression models were used.

##### RESULTS:

In white subjects, MVI use was not associated with birth weight, gestational age, or weight-for-gestational-age. However, in black subjects, MVI use was associated with a 536-gram increased birth weight ( $p=0.001$ ). Black MVI users also had longer gestations (although not statistically significant). When birth weights were adjusted for gestational age using z scores, MVI use was associated with increased fetal growth in black infants (+0.86 z score

units, 95% confidence interval: 0.35-1.36).

#### CONCLUSIONS:

The present findings suggest MVI use may improve fetal growth and possibly gestational age in the offspring of African American women.

#### Source

Burris HH, et al. Periconceptional multivitamin use and infant birth weight disparities. *Ann Epidemiol*. 2010 Mar;20(3):233-40.

### A randomized controlled study of effects of dietary magnesium oxide supplementation on bone mineral content in healthy girls

#### ABSTRACT

##### CONTEXT:

The role of magnesium (Mg) as a determinant of bone mass has not been extensively explored. Limited studies suggest that dietary Mg intake and bone mineral density are correlated in adults, but no data from interventional studies in children and adolescents are available.

##### OBJECTIVE:

We sought to determine whether Mg supplementation in periadolescent girls enhances accrual of bone mass.

##### DESIGN:

We carried out a prospective, placebo-controlled, randomized, one-year double-blind trial of Mg supplementation.

##### SETTING:

The study was conducted in the Clinical Research Centers at Yale University School of Medicine.

##### PATIENTS OR OTHER PARTICIPANTS:

Healthy 8- to 14-yr-old Caucasian girls were recruited from community pediatricians' offices. Dietary diaries from over 120 volunteers were analyzed, and those with dietary Mg intake of less than 220 mg/d were invited to participate in the intervention.

##### INTERVENTION:

Magnesium (300 mg elemental Mg per day in two divided doses) or placebo was given orally for 12 months.

##### MAIN OUTCOME MEASURE:

The primary outcome measure was interval

change in bone mineral content (BMC) of the total hip, femoral neck, Ward's area, and lumbar spine (L1-L4) after 12 months of Mg supplementation.

##### RESULTS:

Significantly increased accrual ( $P = 0.05$ ) in integrated hip BMC occurred in the Mg-supplemented vs. placebo group. Trends for a positive Mg effect were evident in the pre- and early puberty and in mid-late puberty. Lumbar spinal BMC accrual was slightly (but not significantly) greater in the Mg-treated group. Compliance was excellent; 73% of capsules were ingested as inferred by pill counts. Serum mineral levels, calciotropic hormones, and bone markers were similar between groups.

##### CONCLUSIONS:

Oral Mg oxide capsules are safe and well tolerated. A positive effect of Mg supplementation on integrated hip BMC was evident in this small cohort.

#### Source

Carpenter TO, et al. A randomized controlled study of effects of dietary magnesium oxide supplementation on bone mineral content in healthy girls. *J Clin Endocrinol Metab*. 2006 Dec;91(12):4866-72.

### Antenatal and Postnatal Iron Supplementation and Childhood Mortality in Rural Nepal: A Prospective Follow-up in a Randomized, controlled Community Trial

#### ABSTRACT

The long-term benefits of antenatal iron supplementation in child survival are not known. In 1999-2001, 4,926 pregnant women in rural Nepal participated in a cluster-randomized, double-masked, controlled trial involving 4 alternative combinations of micronutrient supplements, each containing vitamin A. The authors examined the impact on birth weight and early infant mortality in comparison with controls, who received vitamin A only. They followed the surviving offspring of these women at approximately age 7 years to study effects of in utero supplementation on

survival. Of 4,130 livebirths, 209 infants died in the first 3 months and 8 were lost to follow-up. Of those remaining, 3,761 were followed, 150 died between ages 3 months and 7 years, and 152 were lost to follow-up. Mortality rates per 1,000 child-years from birth to age 7 years differed by maternal supplementation group, as follows: folic acid, 13.4; folic acid-iron, 10.3; folic acid-iron-zinc, 12.0; multiple micronutrients, 14.0; and controls, 15.2. Hazard ratios were 0.90 (95% confidence interval (CI): 0.65, 1.22), 0.69 (95% CI: 0.49, 0.99), 0.80 (95% CI: 0.58, 1.11), and 0.93 (95% CI: 0.66, 1.31), respectively, in the 4 supplementation groups. Maternal iron-folic acid supplementation reduced mortality among these children by 31% between birth and age 7 years. These results provide additional motivation for strengthening antenatal iron-folic acid programs.

#### Source

Christian P, et al. Antenatal and Postnatal Iron Supplementation and Childhood Mortality in Rural Nepal: A Prospective Follow-up in a Randomized, controlled Community Trial. *Am J of Epid.* 2009 Sep;170 (9): 1127-1136.

### Calcium and vitamin-D supplementation on bone structural properties in peripubertal female identical twins: a randomized controlled trial

#### ABSTRACT

A randomised controlled trial was used in assessing the impact of 6 months of daily calcium and vitamin-D supplementation on trabecular and cortical bone acquisition at distal tibial and radial sites using peripheral quantitative computed tomography (pQCT). Daily supplementation was associated with increased bone density and bone strength at the distal tibia and radius.

#### INTRODUCTION:

pQCT has not been used to assess bone responses to calcium and vitamin-D supplementation on peripubertal children. This randomised controlled trial aimed to assess the impact of a 6-month daily calcium and vitamin-D supplementation on trabecular and cortical bone acquisition at distal tibial and radial sites using pQCT.

#### METHODS:

Twenty pairs of peripubertal female identical twins, aged 9 to 13 years, were randomly assigned to receive either 800 mg of calcium and 400 IU of vitamin D3, or a matched placebo. Bone structural properties at the distal tibia and distal radius were acquired at baseline and 6 months.

#### RESULTS:

The calcium-supplemented group showed greater gains in trabecular density, trabecular area and strength strain index at the 4% of distal tibial and radial sites compared with the placebo group ( $p=0.001$ ). Greater gains in cortical area at the 38% and 66% of tibial sites were also found in twins receiving the calcium supplement ( $p=0.001$ ).

#### CONCLUSIONS:

Daily supplementation for a period of 6 months was associated with increased trabecular area, trabecular density and strength strain index at the ultra-distal tibia and radius and increased cortical area at tibial mid-shaft.

#### Source

Greene DA, et al. Calcium and vitamin-D supplementation on bone structural properties in peripubertal female identical twins: a randomized controlled trial. *osteoporos Int.* 2011 Feb;22(2):489-98. Epub 2010 Jun 11.

### Mild iodine deficiency during pregnancy is associated with reduced educational outcomes in the offspring: 9-year follow-up of the gestational iodine cohort

#### ABSTRACT

#### CONTEXT:

Severe iodine deficiency (ID) during gestation is associated with neurocognitive sequelae. The long-term impact of mild ID, however, has not been well characterized.

#### OBJECTIVE:

The purpose of this study was to determine whether children born to mothers with urinary iodine concentrations (UICs)  $<150 \mu\text{g/L}$  during pregnancy have poorer educational outcomes in primary school than peers whose mothers did not have gestational ID (UIC  $\geq 150 \mu\text{g/L}$ ).

#### DESIGN:

This was a longitudinal follow-up (at 9 years old) of the Gestational Iodine Cohort. Pregnancy occurred during a period of mild ID in the population, with the children subsequently growing up in an iodine-replete environment.

#### SETTING AND PARTICIPANTS:

Participants were children whose mothers attended The Royal Hobart Hospital (Tasmania) antenatal clinics between 1999 and 2001.

#### MAIN OUTCOME MEASURES:

Australian national curriculum and Tasmanian state curriculum educational assessment data for children in year 3 were analyzed.

#### RESULTS:

Children whose mothers had UIC  $<150 \mu\text{g/L}$  had reductions of 10.0% in spelling ( $-41.1$  points, 95% confidence interval [CI],  $-68.0$  to  $-14.3$ ,  $P = .003$ ), 7.6% in grammar ( $-30.9$  points, 95% CI,  $-60.2$  to  $-1.7$ ,  $P = .038$ ), and 5.7% in English-literacy ( $-0.33$  points, 95% CI,  $-0.63$  to  $-0.03$ ,  $P = .034$ ) performance compared with children whose mothers' UICs were  $\geq 150 \mu\text{g/L}$ . These associations remained significant after adjustment for a range of biological factors (maternal age at birth of child, gestational length at time of birth, gestational age at time of urinary iodine collection, birth weight, and sex). Differences in spelling remained significant after further adjustment for socioeconomic factors (maternal occupation and education).

#### CONCLUSIONS:

This study provides preliminary evidence that even mild iodine deficiency during pregnancy can have long-term adverse impacts on fetal neurocognition that are not ameliorated by iodine sufficiency during childhood.

#### Source

Hynes KL, Otahal P, Hay I, Burgess JR. Mild iodine deficiency during pregnancy is associated with reduced educational outcomes in the offspring: 9-year follow-up of the gestational iodine cohort. *J Clin Endocrinol Metab.* 2013;98(5):1954-62.



## Folate and neural tube defects

### ABSTRACT

A protective effect of folate against the development of neural tube defects (NTDs), specifically, anencephaly and spina bifida, is now well recognized, having been established by a chain of clinical research studies over the past half century. This article summarizes the more important of these studies, which have led to the current situation in which all women capable of becoming pregnant are urged to ingest folic acid regularly. The recommended intakes are 4 mg/d for those at high risk (by virtue of a previous NTD pregnancy outcome) and 0.4 mg/d for all others. However, a reduction in NTD births did not follow promulgation of these recommendations, and so folic acid fortification was mandated in the United States and some other countries. Although some controversy remains about the adequacy of fortification levels, the process was followed by significant improvement in folate indexes and a reduction of 25-30% in NTD frequency (about one-half of the proportion of cases assumed to be responsive to folate). The folate-NTD relation represents the only instance in which a congenital malformation can be prevented simply and consistently. Nevertheless, several research gaps remain: identification of the mechanism by which the defect occurs and how folate ameliorates it; characterization of the relative efficacy of food folate, folic acid added to foods, and folic acid by itself; delineation of the dose-response relations of folate and NTD prevention; and more precise quantification of the dose needed to prevent recurrences.

### Source

Pitkin RM. Folate and neural tube defects. *Am J Clin Nutr* 2007; 85(1): 285S-288S.

## Lower maternal folate status in early pregnancy is associated with childhood hyperactivity and peer problems in offspring

### ABSTRACT

#### BACKGROUND:

Maternal nutrition during pregnancy has been linked with fetal brain development and psychopathology in the offspring. We examined for associations of maternal folate status and dietary intake during pregnancy with brain growth and childhood behavioural difficulties in the offspring.

#### METHODS:

In a prospective cohort study, maternal red blood cell folate (RCF) was measured at 14 weeks of pregnancy and total folate intake (TFI) from food and supplements was assessed in early and late pregnancy. The offspring's head circumference and body weight were measured at birth and in infancy, and 100 mothers reported on children's behavioural difficulties at a mean age of 8.75 years using the Strengths and Difficulties Questionnaire.

#### RESULTS:

Lower maternal RCF and TFI in early pregnancy were associated with higher childhood hyperactivity (RCF: beta = -.24; p = .013; TFI: beta = -.24; p = .022) and peer problems scores (RCF: beta = -.28; p = .004; TFI: beta = -.28; p = .009) in the offspring. Maternal gestational RCF was positively associated with head circumference at birth (adjusted for gestational age), and mediation analyses showed significant inverse indirect associations of RCF with hyperactivity/inattention and peer problems via fetal brain growth. Adjustment for mother's smoking and drinking alcohol during pregnancy did not change the results.

#### CONCLUSIONS:

Although the associations are small and residual confounding is possible, our data provide preliminary support for the hypothesis that lower folate status in early pregnancy might impair fetal brain development and affect hyperactivity/inattention and peer problems in childhood.

### Source

Schlotz W, et al. Lower maternal folate status in early pregnancy is associated with childhood hyperactivity and peer problems in offspring. *J Child Psychol Psychiatry*. 2010 May;51(5):594-602.

## Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren

### ABSTRACT

#### BACKGROUND:

To our knowledge, no rigorously designed clinical trials have evaluated the relation between vitamin D and physician-diagnosed seasonal influenza.

#### OBJECTIVE:

We investigated the effect of vitamin D supplements on the incidence of seasonal influenza A in schoolchildren.

#### DESIGN:

From December 2008 through March 2009, we conducted a randomized, double-blind, placebo-controlled trial comparing vitamin D(3) supplements (1200 IU/d) with placebo in schoolchildren. The primary outcome was the incidence of influenza A, diagnosed with influenza antigen testing with a nasopharyngeal swab specimen.

#### RESULTS:

Influenza A occurred in 18 of 167 (10.8%) children in the vitamin D(3) group compared with 31 of 167 (18.6%) children in the placebo group [relative risk (RR), 0.58; 95% CI: 0.34, 0.99; P = 0.04].

The reduction in influenza A was more prominent in children who had not been taking other vitamin D supplements (RR: 0.36; 95% CI: 0.17, 0.79; P = 0.006) and who started nursery school after age 3 y (RR: 0.36; 95% CI: 0.17, 0.78; P = 0.005). In children with a previous diagnosis of asthma, asthma attacks as a secondary outcome occurred in 2 children receiving vitamin D(3) compared with 12 children receiving placebo (RR: 0.17; 95% CI: 0.04, 0.73; P = 0.006).

#### CONCLUSION:

This study suggests that vitamin D(3) supplementation during the winter may reduce the incidence of influenza A, especially in specific subgroups of schoolchildren. This trial was registered at <https://center.umin.ac.jp> as UMIN000001373.

### Source

Urashima M, et al. Randomized trial

of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. *Am J Clin Nutr.* 2010 May;91(5):1255-60.

**Folic Acid Supplementation for the Prevention of Neural Tube Defects: An Update of the Evidence for the U.S. Preventive Services Task Force Rockville (MD): Agency for Healthcare Research and Quality (US)**

**ABSTRACT**

**BACKGROUND:**

Neural tube defects (NTDs) are among the most common birth defects in the United States.

**PURPOSE:**

To update the evidence on folic acid supplementation in women of childbearing age for the prevention of neural tube defects in their offspring.

**DATA SOURCES:**

MEDLINE and Cochrane Library searches (from January 1995 through November 2007), recent systematic reviews, reference lists of retrieved articles, and expert suggestions.

**STUDY SELECTION:**

English language studies were selected to answer the following two questions: Does folic acid supplementation in women of childbearing age reduce the risk of a pregnancy affected by a neural tube defect? Does folic acid supplementation in women of childbearing age increase the risk of any harmful outcomes for either the woman or the infant? The following study types were selected: for potential benefits of folic acid—randomized, controlled trials (RCTs), case-control studies, cohort studies, systematic reviews and meta-analyses; for potential harms of folic acid—RCTs, case-control studies, systematic reviews, meta-analyses, and large observational studies.

**DATA EXTRACTION:**

All studies were reviewed, abstracted, and rated for quality using predefined U.S. Preventive Services Task Force criteria. Data Synthesis: Four observational studies reported benefit, in reduction of risk of NTD associated with folic acid-containing supplements. Differences in study type and methods

prevent the calculation of a summary of the reduction in risk. The one included study on harms reported that the association of twinning with folic acid intake disappeared after adjusting for in vitro fertilization and for underreporting of folic acid intake.

**LIMITATIONS:**

There is limited evidence on dose. We found no evidence on the potential harm of masking vitamin B12 deficiency in women of childbearing age. Our search focused on NTDs and therefore does not provide a comprehensive review of the effects of folic acid on all possible outcomes.

**CONCLUSIONS:**

New observational evidence supports previous RCT evidence that folic acid—containing supplements reduce the risk of NTD-affected pregnancies. The association of folic acid use with twin gestation may be confounded by fertility interventions including ovulation stimulation and in vitro fertilization.

**Source**

Wolff T, Witkop CT, Miller T, Syed SB. Folic Acid Supplementation for the Prevention of Neural Tube Defects: An Update of the Evidence for the U.S. Preventive Services Task Force Rockville (MD): Agency for Healthcare Research and Quality (US); 2009 May. R

**COGNITIVE HEALTH**

**Nutraceuticals in the treatment of obsessive compulsive disorder (OCD): A review of mechanistic and clinical evidence**

**ABSTRACT**

Obsessive-compulsive disorder (OCD) is a debilitating mental illness which has a significant impact on quality of life. First-line SSRI treatments for OCD typically are of limited benefit to only 40-60% of patients, and are associated with a range of adverse side effects. Current preclinical research investigating nutraceuticals (natural products) for OCD, reveals encouraging novel activity in modulating key pathways suggested to be involved in

the pathogenesis of OCD (glutamatergic and serotonergic pathway dysregulation). Emerging clinical evidence also appears to tentatively support certain nutrients and plant-based interventions with known active constituents which modulate these pathways: N-acetylcysteine, myo-inositol, glycine, and milk thistle (*Silybum marianum*). The serotonin precursor tryptophan is unlikely to be of use in treating OCD while 5-HTP may possibly be a more effective precursor strategy. However, there is currently no clinical evidence to test the efficacy of either of these substances. Currently the balance of clinical evidence does not support the use of St. John's wort (*Hypericum perforatum*) in OCD. While clinical research in this area is in its infancy, further research into nutraceuticals is warranted in light of the promising preclinical data regarding their mechanisms of action and their favourable side effect profiles in comparison to current SSRI treatments. It is recommended that future clinical trials of nutraceutical treatments for OCD utilize randomized placebo-controlled study designs and considerably larger sample sizes in order to properly test for efficacy.

**Source**

Camfield DA, Sarris J, Berk M. Nutraceuticals in the treatment of obsessive compulsive disorder (OCD): A review of mechanistic and clinical evidence. *Prog Neuro-Psychopharmacol Biol Psychiatry* (2011), doi:10.1016/j.pnpbp.2011.02.011

**Inositol—clinical applications for exogenous use**

**ABSTRACT**

Recent advances in nutritional and biochemical research have documented inositol as an important dietary and cellular constituent. The processes involved in inositol metabolism and its derivatives in the tissues of mammals have been characterized in vivo as well as at the enzymatic level. Biochemical

functions defined for phosphatidylinositol in biological membranes include the regulation of cellular responses to external stimuli and/or nerve transmission as well as the mediation of enzyme activity through interactions with various specific proteins. Altered production of inositol has been documented in patients with diabetes mellitus, chronic renal failure, galactosemia, and multiple sclerosis. Inositol has been reported to be effective in treating central nervous system disorders such as depression, Alzheimer's disease, panic disorder, and obsessive-compulsive disorder. It has documented benefit for use in pediatric respiratory depression syndrome. In addition, recent studies have evaluated its usefulness as an analgesic. Inositol has been studied extensively as potential treatment to alleviate some negative effects associated with lithium therapy. The use of inositol in pregnant women remains controversial. Although its benefit in preventing neural tube defects in embryonic mice is documented, the risk of inducing uterine contractions limits its usefulness in pregnancy.

#### Source

Colodny L, Hoffman RL. Inositol—clinical applications for exogenous use. *Altern Med Rev* 1998;3(5):432-47.

### **Cognitive and clinical outcomes of homocysteine-lowering B-vitamin treatment in mild cognitive impairment: a randomized controlled trial**

#### ABSTRACT

##### **BACKGROUND:**

Homocysteine is a risk factor for Alzheimer's disease. In the first report on the VITACOG trial, we showed that homocysteine-lowering treatment with B vitamins slows the rate of brain atrophy in mild cognitive impairment (MCI). Here we report the effect of B vitamins on cognitive and clinical decline (secondary outcomes) in the same study.

##### **METHODS:**

This was a double-blind, single-centre study, which included participants with MCI, aged  $\geq 70$  y, randomly assigned to

receive a daily dose of 0.8 mg folic acid, 0.5 mg vitamin B(12) and 20 mg vitamin B(6) (133 participants) or placebo (133 participants) for 2 y. Changes in cognitive or clinical function were analysed by generalized linear models or mixed-effects models.

##### **RESULTS:**

The mean plasma total homocysteine was 30% lower in those treated with B vitamins relative to placebo. B vitamins stabilized executive function (CLOX) relative to placebo ( $P = 0.015$ ). There was significant benefit of B-vitamin treatment among participants with baseline homocysteine above the median ( $11.3 \mu\text{mol/L}$ ) in global cognition (Mini Mental State Examination,  $P < 0.001$ ), episodic memory (Hopkins Verbal Learning Test-delayed recall,  $P = 0.001$ ) and semantic memory (category fluency,  $P = 0.037$ ). Clinical benefit occurred in the B-vitamin group for those in the upper quartile of homocysteine at baseline in global clinical dementia rating score ( $P = 0.02$ ) and IQCODE score ( $P = 0.01$ ).

##### **CONCLUSION:**

In this small intervention trial, B vitamins appear to slow cognitive and clinical decline in people with MCI, in particular in those with elevated homocysteine. Further trials are needed to see if this treatment will slow or prevent conversion from MCI to dementia.

#### Source

de Jager CA et al. Cognitive and clinical outcomes of homocysteine-lowering B-vitamin treatment in mild cognitive impairment: a randomized controlled trial. *Int J Geriatr Psychiatry* [Epub ahead of print, July, 2011]

### **Preventing Alzheimer's disease-related gray matter atrophy by B-vitamin treatment**

#### ABSTRACT

Is it possible to prevent atrophy of key brain regions related to cognitive decline and Alzheimer's disease (AD)? One approach is to modify nongenetic risk factors, for instance by lowering elevated plasma homocysteine using B vitamins. In an initial,

randomized controlled study on elderly subjects with increased dementia risk (mild cognitive impairment according to 2004 Petersen criteria), we showed that high-dose B-vitamin treatment (folic acid 0.8 mg, vitamin B6 20 mg, vitamin B12 0.5 mg) slowed shrinkage of the whole brain volume over 2 y. Here, we go further by demonstrating that B-vitamin treatment reduces, by as much as seven fold, the cerebral atrophy in those gray matter (GM) regions specifically vulnerable to the AD process, including the medial temporal lobe. In the placebo group, higher homocysteine levels at baseline are associated with faster GM atrophy, but this deleterious effect is largely prevented by B-vitamin treatment. We additionally show that the beneficial effect of B vitamins is confined to participants with high homocysteine (above the median,  $11 \mu\text{mol/L}$ ) and that, in these participants, a causal Bayesian network analysis indicates the following chain of events: B vitamins lower homocysteine, which directly leads to a decrease in GM atrophy, thereby slowing cognitive decline. Our results show that B-vitamin supplementation can slow the atrophy of specific brain regions that are a key component of the AD process and that are associated with cognitive decline. Further B-vitamin supplementation trials focusing on elderly subjects with high homocysteine levels are warranted to see if progression to dementia can be prevented.

#### Source

Douaud G. et. al. Preventing Alzheimer's disease-related gray matter atrophy by B-vitamin treatment. *PNAS* 2013;119(23):9523-9528.

### **A Multi-nutrient supplement reduced markers of inflammation and improved physical performance in active individuals of middle to older age: a randomized, double-blind, placebo-controlled study**

#### ABSTRACT

##### **BACKGROUND:**

While exercise acts to combat inflammation and aging, the ability to exercise may itself be compromised by inflammation and inflammation's impact on muscle recovery and joint inflammation. A number of nutritional supplements have been shown to reduce inflammation and improve recovery. The purpose of the current investigation was to examine the effect of a multi-nutrient supplement containing branched chain amino acids, taurine, anti-inflammatory plant extracts, and B vitamins on inflammatory status, endothelial function, physical function, and mood in middle-aged individuals.

#### **METHODS:**

Thirty-one healthy and active men (N = 16, mean age  $56 \pm 6.0$  yrs) and women (N = 15, mean age =  $52 \pm 7.5$  yrs) participated in this investigation. Subjects completed one 28 day cycle of placebo supplementation and one 28 day cycle of multi-nutrient supplementation (separated by a one week washout period) in a balanced, randomized, double-blind, cross-over design. Subjects completed weekly perceptual logs (PROMIS-57, KOOS) and pre- and post-testing around the supplementation period. Testing consisted of brachial artery flow mediated dilation (FMD), blood measures, and physical performance on vertical jump, handgrip strength, and balance (dispersion from center of pressure). Significance for the investigation was  $p \leq 0.05$ .

#### **RESULTS:**

IL-6 significantly decreased in both men (from  $1.2 \pm 0.2$  to  $0.7 \pm 0.4$  pg·mL<sup>-1</sup>) and women (from  $1.16 \pm 0.04$  to  $0.7 \pm 0.4$  pg·mL<sup>-1</sup>). Perceived energy also improved for both men (placebo:  $1.8 \pm 0.7$ ; supplement:  $3.7 \pm 0.8$  AUC) and women (placebo:  $1.2 \pm 0.7$ ; supplement:  $2.8 \pm 0.8$  AUC). Alpha-1-antichymotrypsin (from  $108.9 \pm 38.6$  to  $55.5 \pm 22.2$  ug·mL<sup>-1</sup>), Creatine Kinase (from  $96 \pm 34$  to  $67 \pm 23$  IU·L<sup>-1</sup>), general pain, and joint pain decreased in men only, while anxiety and balance (from  $0.52 \pm 0.13$  to  $0.45 \pm 0.12$  cm) improved in women only. Men showed increased performance in vertical jump power (from  $2642 \pm 244$  to  $3134 \pm 282$  W) and grip strength (from  $42.1 \pm 5.9$  to  $48.5 \pm 4.9$  kg).

#### **CONCLUSIONS:**

A multi-nutrient supplement is effective in improving inflammatory status in both men and women, markers of pain, joint pain, strength, and power in men only, and both anxiety and balance (a risk factor for hip fracture) in women. Therefore, a multi-nutrient supplement may help middle-aged individuals to prolong physical function and maintain a healthy, active lifestyle.

#### **Source**

Dunn-Lewis C et al. A Multi-nutrient supplement reduced markers of inflammation and improved physical performance in active individuals of middle to older age: a randomized, double-blind, placebo-controlled study. Nutr J 10:90, 2011.

#### **Effects of dietary supplements on depressive symptoms in older patients: A randomized double-blind placebo-controlled trial**

#### **ABSTRACT**

##### **BACKGROUND & AIMS:**

The effect of nutritional supplements on mental health in older patients has received little attention so far. The aims of this trial were therefore to test the effect of nutritional support on older patient's depressive symptoms and cognitive function.

##### **METHODS:**

In this prospective, double-blind, placebo-controlled study, we randomly assigned 225 hospitalised acutely ill older patients to receive either normal hospital diet plus 400 mL oral nutritional supplements (106 subjects) or normal hospital diet plus a placebo (119 subjects) daily for 6 weeks. The composition of the supplement was such as to provide 995 kcal for energy and 100% of the Reference Nutrient Intakes for a healthy old person for vitamins and minerals. Outcome measures were 6 weeks and 6 months changes in nutritional status, depressive symptoms and cognitive state.

##### **RESULTS:**

Randomisation to the supplement group led to a significant increase in red-cell folate and plasma vitamin B12 concentrations,

in contrast to a decrease seen in the placebo group. There were significant differences in symptoms of depression scores in the supplement group compared with the placebo group at 6 months ( $p = 0.021$  for between groups difference). The effect of supplement was seen in all patient groups including those with no symptoms of depression, mild depression and those with severe depression ( $p = 0.007$ ). There was no evidence of a difference in cognitive function scores at 6 months.

##### **CONCLUSION:**

Oral nutritional supplementation of hospitalised acutely ill older patients led to a statistically significant benefit on depressive symptoms.

#### **Source**

Gariballa S and Forster S. Effects of dietary supplements on depressive symptoms in older patients: A randomized double-blind placebo-controlled trial. Clinical Nutrition 26:545-51, 2007.

#### **Effects of high-dose B vitamin complex with vitamin C and minerals on subjective mood and performance in healthy males**

#### **ABSTRACT**

##### **RATIONALE:**

A significant proportion of the general population report supplementing their diet with one or more vitamins or minerals, with common reasons for doing so being to combat stress and fatigue and to improve mental functioning. Few studies have assessed the relationship between supplementation with vitamins/minerals and psychological functioning in healthy cohorts of non-elderly adults.

##### **OBJECTIVES:**

The present randomised, placebo-controlled, double-blind, parallel groups trial assessed the cognitive and mood effects of a high-dose B-complex vitamin and mineral supplement (Berocca®) in 215 males aged 30 to 55 years, who were in full-time employment.

##### **METHODS:**

Participants attended the laboratory



prior to and on the last day of a 33-day treatment period where they completed the Profile of Mood States (POMS), Perceived Stress Scale (PSS) and General Health Questionnaire (GHQ-12). Cognitive performance and task-related modulation of mood/fatigue were assessed with the 60 min cognitive demand battery. On the final day, participants also completed the Stroop task for 40 min whilst engaged in inclined treadmill walking and subsequent executive function was assessed.

#### RESULTS:

Vitamin/mineral supplementation led to significant improvements in ratings on the PSS, GHQ-12 and the 'vigour' subscale of the POMS. The vitamin/mineral group also performed better on the Serial 3s subtractions task and rated themselves as less 'mentally tired' both pre- and post-completion of the cognitive demand battery.

#### CONCLUSIONS:

Healthy members of the general population may benefit from augmented levels of vitamins/minerals via direct dietary supplementation. Specifically, supplementation led to improved ratings of stress, mental health and vigour and improved cognitive performance during intense mental processing.

#### Source

Kennedy DO et al. Effects of high-dose B vitamin complex with vitamin C and minerals on subjective mood and performance in healthy males. *Psychopharmacol* 211:55-68, 2010.

#### Serum 25-Hydroxyvitamin D Concentration and Cognitive Impairment

#### ABSTRACT

Vitamin D may be of interest in the prevention of cognitive impairment, though previous findings are inconclusive. Participants were 1766 adults aged 65 years and older from the Health Survey for England 2000, a nationally representative population-based study. Cognitive impairment was assessed using the Abbreviated Mental Test

Score. The cross-sectional relation of serum 25-hydroxyvitamin D quartiles to cognitive impairment was modeled using logistic regression. In all, 212 participants (12%) were cognitively impaired. Odds ratios (95% confidence intervals) for cognitive impairment in the first (8-30 nmol/L), second (31-44 nmol/L), and third (45-65 nmol/L) quartiles of serum 25-hydroxyvitamin D compared with the fourth (66-170 nmol/L) were 2.3 (1.4-3.8), 1.4 (0.8-2.4), and 1.1 (0.6-1.9), after adjustment for age, sex, education, ethnicity, season of testing, and additional risk factors for cognitive impairment ( $P$  for linear trend = .001). Our data suggest low serum 25-hydroxyvitamin D is associated with increased odds of cognitive impairment.

#### Source

Llewellyn DJ, et al. Serum 25-Hydroxyvitamin D Concentration and Cognitive Impairment. *J Geriatr Psychiatry Neurol*. 2009 Feb; 22 (3): 188-95.

#### Homocysteine-lowering by B vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: A randomized controlled trial

#### ABSTRACT

##### BACKGROUND:

An increased rate of brain atrophy is often observed in older subjects, in particular those who suffer from cognitive decline. Homocysteine is a risk factor for brain atrophy, cognitive impairment and dementia. Plasma concentrations of homocysteine can be lowered by dietary administration of B vitamins.

##### OBJECTIVE:

To determine whether supplementation with B vitamins that lower levels of plasma total homocysteine can slow the rate of brain atrophy in subjects with mild cognitive impairment in a randomised controlled trial (VITACOG, <https://clinicaltrials.gov/ct2/show/study?term=VITACOG&rank=1> ISRCTN94410159).

##### METHODS AND FINDINGS:

Single-center, randomized, double-blind controlled trial of high-dose folic acid, vitamins B(6) and B(12) in 271 individuals

(of 646 screened) over 70 y old with mild cognitive impairment. A subset (187) volunteered to have cranial MRI scans at the start and finish of the study. Participants were randomly assigned to two groups of equal size, one treated with folic acid (0.8 mg/d), vitamin B(12) (0.5 mg/d) and vitamin B(6) (20 mg/d), the other with placebo; treatment was for 24 months. The main outcome measure was the change in the rate of atrophy of the whole brain assessed by serial volumetric MRI scans.

#### RESULTS:

A total of 168 participants (85 in active treatment group; 83 receiving placebo) completed the MRI section of the trial. The mean rate of brain atrophy per year was 0.76% [95% CI, 0.63-0.90] in the active treatment group and 1.08% [0.94-1.22] in the placebo group ( $P$  = 0.001). The treatment response was related to baseline homocysteine levels: the rate of atrophy in participants with homocysteine >13  $\mu$ mol/L was 53% lower in the active treatment group ( $P$  = 0.001). A greater rate of atrophy was associated with a lower final cognitive test scores. There was no difference in serious adverse events according to treatment category.

#### CONCLUSIONS AND SIGNIFICANCE:

The accelerated rate of brain atrophy in elderly with mild cognitive impairment can be slowed by treatment with homocysteine-lowering B vitamins. Sixteen percent of those over 70 y old have mild cognitive impairment and half of these develop Alzheimer's disease. Since accelerated brain atrophy is a characteristic of subjects with mild cognitive impairment who convert to Alzheimer's disease, trials are needed to see if the same treatment will delay the development of Alzheimer's disease.

#### TRIAL REGISTRATION:

Controlled-Trials.com ISRCTN94410159.

#### Source

Smith AD, et al. Homocysteine-lowering by B vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: A randomized controlled trial. 2010; *PLoS ONE* 5(9):e12244.

## Vitamin B12, cognition, and brain MRI measures: A crosssectional examination

### Abstract

#### OBJECTIVE:

To investigate the interrelations of serum vitamin B12 markers with brain volumes, cerebral infarcts, and performance in different cognitive domains in a biracial population sample cross-sectionally.

#### METHODS:

In 121 community-dwelling participants of the Chicago Health and Aging Project, serum markers of vitamin B12 status were related to summary measures of neuropsychological tests of 5 cognitive domains and brain MRI measures obtained on average 4.6 years later among 121 older adults.

#### RESULTS:

Concentrations of all vitamin B12-related markers, but not serum vitamin B12 itself, were associated with global cognitive function and with total brain volume. Methylmalonate levels were associated with poorer episodic memory and perceptual speed, and cystathionine and 2-methylcitrate with poorer episodic and semantic memory. Homocysteine concentrations were associated with decreased total brain volume. The homocysteine-global cognition effect was modified and no longer statistically significant with adjustment for white matter volume or cerebral infarcts. The methylmalonate-global cognition effect was modified and no longer significant with adjustment for total brain volume.

#### CONCLUSIONS:

Methylmalonate, a specific marker of B12 deficiency, may affect cognition by reducing total brain volume whereas the effect of homocysteine (nonspecific to vitamin B12 deficiency) on cognitive performance may be mediated through increased white matter hyperintensity and cerebral infarcts. Vitamin B12 status may affect the brain through multiple mechanisms.

### Source

Tangney CC et al. Vitamin B12, cognition, and brain MRI measures: A crosssectional

examination. *Neurol* 77:1276-82, 2011.

## DIGESTIVE HEALTH

### Optimal vitamin D status for colorectal cancer prevention: a quantitative meta analysis

### ABSTRACT

#### BACKGROUND:

Previous studies, such as the Women's Health Initiative, have shown that a low dose of vitamin D did not protect against colorectal cancer, yet a meta-analysis indicates that a higher dose may reduce its incidence.

#### METHODS:

Five studies of serum 25(OH)D in association with colorectal cancer risk were identified using PubMed. The results of all five serum studies were combined using standard methods for pooled analysis. The pooled results were divided into quintiles with median 25(OH)D values of 6, 16, 22, 27, and 37 ng/mL. Odds ratios were calculated by quintile of the pooled data using Peto's Assumption-Free Method, with the lowest quintile of 25(OH)D as the reference group. A dose-response curve was plotted based on the odds for each quintile of the pooled data. Data were abstracted and analyzed in 2006.

#### RESULTS:

Odds ratios for the combined serum 25(OH)D studies, from lowest to highest quintile, were 1.00, 0.82, 0.66, 0.59, and 0.46 ( $p(\text{trend}) < 0.0001$ ) for colorectal cancer. According to the DerSimonian-Laird test for homogeneity of pooled data, the studies were homogeneous ( $\chi^2 = 1.09$ ,  $df = 4$ ,  $p = 0.90$ ). The pooled odds ratio for the highest quintile versus the lowest was 0.49 ( $p < 0.0001$ , 95% confidence interval, 0.35-0.68). A 50% lower risk of colorectal cancer was associated with a serum 25(OH)D level  $> \text{or} = 33 \text{ ng/mL}$ , compared to  $< \text{or} = 12 \text{ ng/mL}$ .

#### CONCLUSIONS:

The evidence to date suggests that daily intake of 1000-2000 IU/day of vitamin D(3) could reduce the incidence of colorectal with minimal risk.

### Source

Gorham ED, et al. Optimal vitamin D status for colorectal cancer prevention: a quantitative meta analysis. *Am J Prev Med*. 2007 Mar;32(3):210-6.

### Vegetables, Fruit, and Colon Cancer in the Iowa Women's Health Study

### ABSTRACT

Previous epidemiologic studies have shown an inverse association between vegetable and fruit consumption and colon cancer risk; few of these studies have been prospective or have focused on women. This report describes results from a prospective cohort study of 41,837 women aged 55-69 years who completed a 127-item food frequency questionnaire in 1986 and were monitored for cancer incidence for 5 years via the State Health Registry of Iowa. After specific exclusion criteria were applied, 212 colon cancer cases and 167,447 person-years were available for analysis. Intakes of 15 vegetable and fruit groups and dietary fiber were the major factors of interest. Consumption of garlic was inversely associated with risk, with an age- and energy-adjusted relative risk of 0.68 (95% confidence interval (CI) 0.46-1.02) for the uppermost versus the lowermost consumption levels. Inverse associations were also observed for intakes of all vegetables and dietary fiber; age- and energy-adjusted relative risks for the uppermost versus the lowermost intake quartiles were 0.73 (95% CI 0.47-1.13) and 0.80 (95% CI 0.49-1.31), respectively. Associations for the other vegetable and fruit groups were less remarkable.

### Source

Steinmetz KA, et al. Vegetables, Fruit, and Colon Cancer in the Iowa Women's Health Study. *Am J Epidemiol*. 1994; 139: 232-235

## EYE HEALTH

**A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8.**

### ABSTRACT

#### BACKGROUND:

Observational and experimental data suggest that antioxidant and/or zinc supplements may delay progression of age-related macular degeneration (AMD) and vision loss.

#### OBJECTIVE:

To evaluate the effect of high-dose vitamins C and E, beta carotene, and zinc supplements on AMD progression and visual acuity.

#### DESIGN:

The Age-Related Eye Disease Study, an 11-center double-masked clinical trial, enrolled participants in an AMD trial if they had extensive small drusen, intermediate drusen, large drusen, noncentral geographic atrophy, or pigment abnormalities in 1 or both eyes, or advanced AMD or vision loss due to AMD in 1 eye. At least 1 eye had best-corrected visual acuity of 20/32 or better. Participants were randomly assigned to receive daily oral tablets containing: (1) antioxidants (vitamin C, 500 mg; vitamin E, 400 IU; and beta carotene, 15 mg); (2) zinc, 80 mg, as zinc oxide and copper, 2 mg, as cupric oxide; (3) antioxidants plus zinc; or (4) placebo.

#### MAIN OUTCOME MEASURES:

(1) Photographic assessment of progression to or treatment for advanced AMD and (2) at least moderate visual acuity loss from baseline ( $>$  or  $=$  15 letters). Primary analyses used repeated-measures logistic regression with a significance level of .01, unadjusted for covariates. Serum level measurements, medical histories, and mortality rates were used for safety monitoring.

#### RESULTS:

Average follow-up of the 3640 enrolled study participants, aged 55-80 years, was 6.3 years, with 2.4% lost to follow-up. Comparison with placebo demonstrated a

statistically significant odds reduction for the development of advanced AMD with antioxidants plus zinc (odds ratio [OR], 0.72; 99% confidence interval [CI], 0.52-0.98). The ORs for zinc alone and antioxidants alone are 0.75 (99% CI, 0.55-1.03) and 0.80 (99% CI, 0.59-1.09), respectively. Participants with extensive small drusen, nonextensive intermediate size drusen, or pigment abnormalities had only a 1.3% 5-year probability of progression to advanced AMD. Odds reduction estimates increased when these 1063 participants were excluded (antioxidants plus zinc: OR, 0.66; 99% CI, 0.47-0.91; zinc: OR, 0.71; 99% CI, 0.52-0.99; antioxidants: OR, 0.76; 99% CI, 0.55-1.05). Both zinc and antioxidants plus zinc significantly reduced the odds of developing advanced AMD in this higher-risk group. The only statistically significant reduction in rates of at least moderate visual acuity loss occurred in persons assigned to receive antioxidants plus zinc (OR, 0.73; 99% CI, 0.54-0.99). No statistically significant serious adverse effect was associated with any of the formulations.

#### CONCLUSIONS:

Persons older than 55 years should have dilated eye examinations to determine their risk of developing advanced AMD. Those with extensive intermediate size drusen, at least 1 large druse, noncentral geographic atrophy in 1 or both eyes, or advanced AMD or vision loss due to AMD in 1 eye, and without contraindications such as smoking, should consider taking a supplement of antioxidants plus zinc such as that used in this study.

#### Source

Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. Arch Ophthalmol

**Clinical trial of lutein in patients with retinitis pigmentosa receiving vitamin A**

### ABSTRACT

#### OBJECTIVE:

To determine whether lutein supplementation will slow visual function decline in patients with retinitis pigmentosa receiving vitamin A.

#### DESIGN:

Randomized, controlled, double-masked trial of 225 nonsmoking patients, aged 18 to 60 years, evaluated over a 4-year interval. Patients received 12 mg of lutein or a control tablet daily. All were given 15,000 IU/d of vitamin A palmitate.

Randomization took into account genetic type and baseline serum lutein level.

#### MAIN OUTCOME MEASURES:

The primary outcome was the total point score for the Humphrey Field Analyzer (HFA) 30-2 program; prespecified secondary outcomes were the total point scores for the 60-4 program and for the 30-2 and 60-4 programs combined, 30-Hz electroretinogram amplitude, and Early Treatment Diabetic Retinopathy Study acuity.

#### RESULTS:

No significant difference in rate of decline was found between the lutein plus vitamin A and control plus vitamin A groups over a 4-year interval for the HFA 30-2 program. For the HFA 60-4 program, a decrease in mean rate of sensitivity loss was observed in the lutein plus vitamin A group ( $P = .05$ ). Mean decline with the 60-4 program was slower among those with the highest serum lutein level or with the highest increase in macular pigment optical density at follow-up ( $P = .01$  and  $P = .006$ , respectively). Those with the highest increase in macular pigment optical density also had the slowest decline in HFA 30-2 and 60-4 combined field sensitivity ( $P = .005$ ). No significant toxic effects of lutein supplementation were observed.

#### CONCLUSION:

Lutein supplementation of 12 mg/d slowed loss of midperipheral visual field on average among nonsmoking adults with retinitis pigmentosa taking vitamin A. Application to Clinical Practice Data are presented that support use of 12 mg/d of lutein to slow visual field loss among nonsmoking adults with retinitis

pigmentosa taking vitamin A.

#### TRIAL REGISTRATION:

ClinicalTrials.gov Identifier: NCT00346333.

#### Source

Berson EL, et al. Clinical trial of lutein in patients with retinitis pigmentosa receiving vitamin A. Arch Ophthalmol. 2010 Apr;128(4):403-11.

### Vitamin D status and early age related macular degeneration in postmenopausal women

#### ABSTRACT

##### OBJECTIVE:

The relationship between serum 25-hydroxyvitamin D (25[OH]D) concentrations (nmol/L) and the prevalence of early age-related macular degeneration (AMD) was investigated in participants of the Carotenoids in Age-Related Eye Disease Study.

##### METHODS:

Stereoscopic fundus photographs, taken from 2001 to 2004, assessed AMD status. Baseline (1994-1998) serum samples were available for 25(OH)D assays in 1313 women with complete ocular and risk factor data. Odds ratios (ORs) and 95% confidence intervals (CIs) for early AMD (n = 241) of 1287 without advanced disease were estimated with logistic regression and adjusted for age, smoking, iris pigmentation, family history of AMD, cardiovascular disease, diabetes, and hormone therapy use.

##### RESULTS:

In multivariate models, no significant relationship was observed between early AMD and 25(OH)D (OR for quintile 5 vs 1, 0.79; 95% CI, 0.50-1.24; P for trend = .47). A significant age interaction (P = .002) suggested selective mortality bias in women aged 75 years and older: serum 25(OH)D was associated with decreased odds of early AMD in women younger than 75 years (n = 968) and increased odds in women aged 75 years or older (n = 319) (OR for quintile 5 vs 1, 0.52; 95% CI, 0.29-0.91; P for trend = .02 and OR, 1.76; 95% CI, 0.77-4.13; P for trend = .05, respectively). Further adjustment for body

mass index and recreational physical activity, predictors of 25(OH)D, attenuated the observed association in women younger than 75 years. Additionally, among women younger than 75 years, intake of vitamin D from foods and supplements was related to decreased odds of early AMD in multivariate models; no relationship was observed with self-reported time spent in direct sunlight.

##### CONCLUSIONS:

High serum 25(OH)D concentrations may protect against early AMD in women younger than 75 years.

#### Source

Millen AE, et al. Vitamin D status and early age related macular degeneration in postmenopausal women. archives of ophthalmology. 2011; 129(4): 481:489. doi:10.1001/archophthalmol.2011.48

### Effects of vitamin D and calcium supplementation on pancreatic B cell function, insulin sensitivity, and glycemia in adults at high risk of diabetes: the Calcium and Vitamin D for Diabetes Mellitus (CaDDM) randomized controlled trial

#### ABSTRACT

##### BACKGROUND:

A suboptimal vitamin D and calcium status has been associated with higher risk of type 2 diabetes in observational studies, but evidence from trials is lacking.

##### OBJECTIVE:

We determined whether vitamin D supplementation, with or without calcium, improved glucose homeostasis in adults at high risk of diabetes.

##### DESIGN:

Ninety-two adults were randomly assigned in a 2-by-2 factorial-design, double-masked, placebo-controlled trial to receive either cholecalciferol (2000 IU once daily) or calcium carbonate (400 mg twice daily) for 16 wk. The primary outcome was the change in pancreatic  $\beta$  cell function as measured by the disposition index after an intravenous-glucose-tolerance test. Other outcomes were acute insulin response, insulin sensitivity, and measures

of glycemia.

##### RESULTS:

Participants had a mean age of 57 y, a body mass index (BMI; in kg/m<sup>2</sup>) of 32, and glycated hemoglobin (Hb A(1c)) of 5.9%. There was no significant vitamin D  $\times$  calcium interaction on any outcomes. The disposition index increased in the vitamin D group and decreased in the no-vitamin D group (adjusted mean change  $\pm$  SE: 300  $\pm$  130 compared with -126  $\pm$  127, respectively; P = 0.011), which was explained by an improvement in insulin secretion (62  $\pm$  39 compared with -36  $\pm$  37 mU  $\cdot$  L(-1)  $\cdot$  min, respectively; P = 0.046). Hb A(1c) increased less, but nonsignificantly, in the vitamin D group than in the no-vitamin D group (0.06  $\pm$  0.03% compared with 0.14  $\pm$  0.03%, respectively; P = 0.081). There was no significant difference in any outcomes with calcium compared with no calcium.

##### CONCLUSION:

In adults at risk of type 2 diabetes, short-term supplementation with cholecalciferol improved  $\beta$  cell function and had a marginal effect on attenuating the rise in Hb A(1c). This trial was registered at clinicaltrials.gov as NCT00436475.

#### Source

Mitri J et al. Effects of vitamin D and calcium supplementation on pancreatic B cell function, insulin sensitivity, and glycemia in adults at high risk of diabetes: the Calcium and Vitamin D for Diabetes Mellitus (CaDDM) randomized controlled trial. Am J

## HEALTHY PREGNANCY

### Vitamin D and gestational diabetes mellitus.

#### ABSTRACT

The incidence of gestational diabetes mellitus (GDM) is increasing worldwide. GDM can be responsible for an important proportion of adverse fetal and maternal outcomes during pregnancy, and it is associated with long-term health deterioration for both mother



and child. Therefore, it is important to identify potentially modifiable risk factors for GDM. Accumulating evidence links vitamin D deficiency with abnormal glucose metabolism, and epidemiological studies have shown that women who develop GDM are more likely to be vitamin D deficient. This review discusses the prevalence, risk factors, and outcomes of GDM and vitamin D deficiency in pregnant women, outlines the possible mechanism of action of vitamin D in glucose homeostasis, and summarizes emerging evidence that associates vitamin D deficiency with the risk of developing GDM. This critical review of the literature indicates there is a need for intervention trials to test the possible beneficial effect of vitamin D supplementation in pregnant women with low vitamin D status to reduce the risk of developing GDM.

#### Source

Alzaim M, Wood RJ. Vitamin D and gestational diabetes mellitus. *Nutr Rev*. 2013 Mar;71(3):158-67.

Periconceptional multivitamin use and infant birth weight disparities

#### ABSTRACT

##### PURPOSE:

In the United States, African American women deliver preterm and low birth weight infants two to three times more frequently than their white counterparts. Our objective was to determine whether maternal periconceptional multivitamin (MVI) use is associated with this disparity.

##### METHODS:

As a secondary analysis of previously collected data from mothers of non-malformed infants from the Slone Epidemiology Center Birth Defects Study, we conducted a retrospective cohort study of 2331 non-Hispanic white and 133 non-Hispanic black mother/infant pairs from 1998 through 2007. To estimate the effect of MVI use on birth outcomes, linear regression models were used.

##### RESULTS:

In white subjects, MVI use was not associated with birth weight, gestational

age, or weight-for-gestational-age. However, in black subjects, MVI use was associated with a 536-gram increased birth weight ( $p=0.001$ ). Black MVI users also had longer gestations (although not statistically significant). When birth weights were adjusted for gestational age using z scores, MVI use was associated with increased fetal growth in black infants (+0.86 z score units, 95% confidence interval: 0.35-1.36).

##### CONCLUSIONS:

The present findings suggest MVI use may improve fetal growth and possibly gestational age in the offspring of African American women.

#### Source

Burris HH, et al. Periconceptional multivitamin use and infant birth weight disparities. *Ann Epidemiol*. 2010 Mar;20(3):233-40.

#### Antenatal and Postnatal Iron

##### Supplementation and Childhood Mortality in Rural Nepal: A Prospective Follow-up in a Randomized, controlled Community Trial

#### ABSTRACT

The long-term benefits of antenatal iron supplementation in child survival are not known. In 1999-2001, 4,926 pregnant women in rural Nepal participated in a cluster-randomized, double-masked, controlled trial involving 4 alternative combinations of micronutrient supplements, each containing vitamin A. The authors examined the impact on birth weight and early infant mortality in comparison with controls, who received vitamin A only. They followed the surviving offspring of these women at approximately age 7 years to study effects of in utero supplementation on survival. Of 4,130 livebirths, 209 infants died in the first 3 months and 8 were lost to follow-up. Of those remaining, 3,761 were followed, 150 died between ages 3 months and 7 years, and 152 were lost to follow-up. Mortality rates per 1,000 child-years from birth to age 7 years differed by maternal supplementation group, as

follows: folic acid, 13.4; folic acid-iron, 10.3; folic acid-iron-zinc, 12.0; multiple micronutrients, 14.0; and controls, 15.2. Hazard ratios were 0.90 (95% confidence interval (CI): 0.65, 1.22), 0.69 (95% CI: 0.49, 0.99), 0.80 (95% CI: 0.58, 1.11), and 0.93 (95% CI: 0.66, 1.31), respectively, in the 4 supplementation groups. Maternal iron-folic acid supplementation reduced mortality among these children by 31% between birth and age 7 years. These results provide additional motivation for strengthening antenatal iron-folic acid programs.

#### Source

Christian P, et al. Antenatal and Postnatal Iron Supplementation and Childhood Mortality in Rural Nepal: A Prospective Follow-up in a Randomized, controlled Community Trial. *Am J of epid*. 2009 Sep;170 (9): 1127-1136.

##### Folate recommendations for pregnancy, lactation, and infancy

#### ABSTRACT

An adequate intake of folate during pregnancy, lactation, and infancy is essential for maternal and child health and normal growth. Higher folate requirements during pregnancy and lactation are difficult to meet by increased intake of folate-rich food products only. Supplementation with folic acid is recommended not only to meet the higher requirements but also to prevent adverse pregnancy outcomes such as neural tube defects (NTDs). In countries that have implemented food fortification with folic acid, the folate intake has raised but does not yet meet the recommended amount for NTD risk reduction. Women's awareness of the need to supplement with folic acid prior to conception shall be raised in all countries. It is under debate whether a high folic acid intake might have metabolic and functional effects in utero and for the infant. Research is needed to investigate potential alternative folate forms for food fortification programs and to test their efficacy in risk reduction of adverse pregnancy outcomes. Breast-

fed infants most likely receive sufficient folate. While the folate level of human milk is simulated in infant formula, data are lacking on the bioavailability and effect of folic acid in infants and on whether a tolerable upper intake level should be defined.

#### Source

Lamers Y (2011). Folate recommendations for pregnancy, lactation, and infancy. *Ann Nutr Metab* 59(1): 32-37.

### Folate and neural tube defects

#### ABSTRACT

A protective effect of folate against the development of neural tube defects (NTDs), specifically, anencephaly and spina bifida, is now well recognized, having been established by a chain of clinical research studies over the past half century. This article summarizes the more important of these studies, which have led to the current situation in which all women capable of becoming pregnant are urged to ingest folic acid regularly. The recommended intakes are 4 mg/d for those at high risk (by virtue of a previous NTD pregnancy outcome) and 0.4 mg/d for all others. However, a reduction in NTD births did not follow promulgation of these recommendations, and so folic acid fortification was mandated in the United States and some other countries. Although some controversy remains about the adequacy of fortification levels, the process was followed by significant improvement in folate indexes and a reduction of 25-30% in NTD frequency (about one-half of the proportion of cases assumed to be responsive to folate). The folate-NTD relation represents the only instance in which a congenital malformation can be prevented simply and consistently. Nevertheless, several research gaps remain: identification of the mechanism by which the defect occurs and how folate ameliorates it; characterization of the relative efficacy of food folate, folic acid added to foods, and folic acid by itself; delineation of the dose-response relations

of folate and NTD prevention; and more precise quantification of the dose needed to prevent recurrences.

#### Source

Pitkin RM. Folate and neural tube defects. *Am J Clin Nutr* 2007; 85(1): 285S-288S.

### Lower maternal folate status in early pregnancy is associated with childhood hyperactivity and peer problems in offspring

#### ABSTRACT

##### BACKGROUND:

Maternal nutrition during pregnancy has been linked with fetal brain development and psychopathology in the offspring. We examined for associations of maternal folate status and dietary intake during pregnancy with brain growth and childhood behavioural difficulties in the offspring.

##### METHODS:

In a prospective cohort study, maternal red blood cell folate (RCF) was measured at 14 weeks of pregnancy and total folate intake (TFI) from food and supplements was assessed in early and late pregnancy. The offspring's head circumference and body weight were measured at birth and in infancy, and 100 mothers reported on children's behavioural difficulties at a mean age of 8.75 years using the Strengths and Difficulties Questionnaire.

##### RESULTS:

Lower maternal RCF and TFI in early pregnancy were associated with higher childhood hyperactivity (RCF: beta = -.24; p = .013; TFI: beta = -.24; p = .022) and peer problems scores (RCF: beta = -.28; p = .004; TFI: beta = -.28; p = .009) in the offspring. Maternal gestational RCF was positively associated with head circumference at birth (adjusted for gestational age), and mediation analyses showed significant inverse indirect associations of RCF with hyperactivity/inattention and peer problems via fetal brain growth. Adjustment for mother's smoking and drinking alcohol during pregnancy did not change the results.

#### CONCLUSIONS:

Although the associations are small and residual confounding is possible, our data provide preliminary support for the hypothesis that lower folate status in early pregnancy might impair fetal brain development and affect hyperactivity/inattention and peer problems in childhood.

#### Source

Schlotz W, et al. Lower maternal folate status in early pregnancy is associated with childhood hyperactivity and peer problems in offspring. *J Child Psychol Psychiatry*. 2010 May;51(5):594-602.

### Maternal vitamin D status as a critical determinant in gestational diabetes

#### ABSTRACT

##### OBJECTIVE:

To synthesize published research to determine the evidence for the association between maternal vitamin D status during pregnancy and the development of gestational diabetes mellitus (GDM).

##### DATA SOURCES:

Literature searches were conducted for data based articles that examined maternal vitamin D during pregnancy, GDM, glucose tolerance, and insulin resistance using the PubMed, CINAHL, and SCOPUS data bases and reference lists from reviewed papers.

##### STUDY SELECTION:

Primary research studies published in the English language between 1999 and 2011 reporting findings regarding the association of vitamin D with glucose homeostasis during pregnancy and GDM.

##### DATA EXTRACTION:

Study characteristics and findings related to vitamin D status determinants, gestational timing, and measures of glucose homeostasis and insulin resistance.

##### DATA SYNTHESIS:

Six data based articles met the criteria for study inclusion. Study findings comprised solely Level-2 evidence for the association of maternal vitamin D deficiency and

risk of GDM. The majority of studies (66%) were conducted between 24 and 30 weeks gestation. Five (83%) studies reported an inverse relationship between circulating vitamin D levels and markers of glucose homeostasis associated with gestational diabetes or an increased risk for GDM associated with reduced maternal levels of vitamin D. In one study, researchers did not identify an association between vitamin D and GDM but did identify an association between higher vitamin D levels and lower fasting glucose and insulin levels.

#### CONCLUSION:

Maternal vitamin D deficiency and insufficiency is prevalent among gravid women and is associated with markers of altered glucose homeostasis. These findings underscore the need for mechanistic and clinical studies to determine optimal vitamin D status in pregnancy for reduction in the risk for GDM with implications for vitamin D supplementation as a potential target for GDM prevention.

#### Source

Senti J, Thiele DK, Anderson CM. Maternal vitamin D status as a critical determinant in gestational diabetes. *J Obstet Gynecol Neonatal Nurs.* 2012;41(3)L 328-38.

#### **Folic Acid Supplementation for the Prevention of Neural Tube Defects: An Update of the Evidence for the U.S. Preventive Services Task Force Rockville (MD): Agency for Healthcare Research and Quality (US)**

#### ABSTRACT

##### BACKGROUND:

Neural tube defects (NTDs) are among the most common birth defects in the United States.

##### PURPOSE:

To update the evidence on folic acid supplementation in women of childbearing age for the prevention of neural tube defects in their offspring.

##### Data Sources:

MEDLINE and Cochrane Library searches (from January 1995 through November 2007), recent systematic reviews, reference

lists of retrieved articles, and expert suggestions.

##### STUDY SELECTION:

English language studies were selected to answer the following two questions: Does folic acid supplementation in women of childbearing age reduce the risk of a pregnancy affected by a neural tube defect? Does folic acid supplementation in women of childbearing age increase the risk of any harmful outcomes for either the woman or the infant? The following study types were selected: for potential benefits of folic acid—randomized, controlled trials (RCTs), case-control studies, cohort studies, systematic reviews and meta-analyses; for potential harms of folic acid—RCTs, case-control studies, systematic reviews, meta-analyses, and large observational studies.

##### DATA EXTRACTION:

All studies were reviewed, abstracted, and rated for quality using predefined U.S. Preventive Services Task Force criteria. Data Synthesis: Four observational studies reported benefit, in reduction of risk of NTD associated with folic acid-containing supplements. Differences in study type and methods prevent the calculation of a summary of the reduction in risk. The one included study on harms reported that the association of twinning with folic acid intake disappeared after adjusting for in vitro fertilization and for underreporting of folic acid intake.

##### LIMITATIONS:

There is limited evidence on dose. We found no evidence on the potential harm of masking vitamin B12 deficiency in women of childbearing age. Our search focused on NTDs and therefore does not provide a comprehensive review of the effects of folic acid on all possible outcomes.

##### CONCLUSIONS:

New observational evidence supports previous RCT evidence that folic acid—containing supplements reduce the risk of NTD-affected pregnancies. The association of folic acid use with twin gestation may be confounded by fertility interventions including ovulation stimulation and in vitro fertilization.

#### Source

Wolff T, Witkop CT, Miller T, Syed SB. Folic Acid Supplementation for the Prevention of Neural Tube Defects: An Update of the Evidence for the U.S. Preventive Services Task Force Rockville (MD): Agency for Healthcare Research and Quality (US); 2009 May. R

#### HEART HEALTH

#### **Cognitive and clinical outcomes of homocysteine-lowering B-vitamin treatment in mild cognitive impairment: a randomized controlled trial**

#### ABSTRACT

##### BACKGROUND:

Homocysteine is a risk factor for Alzheimer's disease. In the first report on the VITACOG trial, we showed that homocysteine-lowering treatment with B vitamins slows the rate of brain atrophy in mild cognitive impairment (MCI). Here we report the effect of B vitamins on cognitive and clinical decline (secondary outcomes) in the same study.

##### METHODS:

This was a double-blind, single-centre study, which included participants with MCI, aged  $\geq 70$  y, randomly assigned to receive a daily dose of 0.8 mg folic acid, 0.5 mg vitamin B(12) and 20 mg vitamin B(6) (133 participants) or placebo (133 participants) for 2 y. Changes in cognitive or clinical function were analysed by generalized linear models or mixed-effects models.

##### RESULTS:

The mean plasma total homocysteine was 30% lower in those treated with B vitamins relative to placebo. B vitamins stabilized executive function (CLOX) relative to placebo ( $P = 0.015$ ). There was significant benefit of B-vitamin treatment among participants with baseline homocysteine above the median (11.3  $\mu\text{mol/L}$ ) in global cognition (Mini Mental State Examination,  $P < 0.001$ ), episodic memory (Hopkins Verbal Learning Test-

delayed recall,  $P = 0.001$ ) and semantic memory (category fluency,  $P = 0.037$ ). Clinical benefit occurred in the B-vitamin group for those in the upper quartile of homocysteine at baseline in global clinical dementia rating score ( $P = 0.02$ ) and IQCODE score ( $P = 0.01$ ).

#### CONCLUSION:

In this small intervention trial, B vitamins appear to slow cognitive and clinical decline in people with MCI, in particular in those with elevated homocysteine. Further trials are needed to see if this treatment will slow or prevent conversion from MCI to dementia.

Source

de Jager CA et al. Cognitive and clinical outcomes of homocysteine-lowering B-vitamin treatment in mild cognitive impairment: a randomized controlled trial. *Int J Geriatr Psychiatry* [Epub ahead of print, July, 2011]

#### Dietary choline and betaine intakes in relationship to concentrations of inflammatory markers in healthy adults: the ATTICA study

#### ABSTRACT

##### BACKGROUND:

Choline and betaine are found in a variety of plant and animal foods and were recently shown to be associated with decreased homocysteine concentrations.

##### OBJECTIVE:

The scope of this work was to investigate the associations between dietary choline and betaine consumption and various markers of low-grade systemic inflammation.

##### DESIGN:

Under the context of a cross-sectional survey that enrolled 1514 men (18-87 y of age) and 1528 women (18-89 y of age) with no history of cardiovascular disease (the ATTICA Study), fasting blood samples were collected and inflammatory markers were measured. Dietary habits were evaluated with a validated food-frequency questionnaire, and the intakes of choline and betaine were calculated from food-composition tables.

#### RESULTS:

Compared with the lowest tertile of choline intake ( $<250$  mg/d), participants who consumed  $>310$  mg/d had, on average, 22% lower concentrations of C-reactive protein ( $P < 0.05$ ), 26% lower concentrations of interleukin-6 ( $P < 0.05$ ), and 6% lower concentrations of tumor necrosis factor- $\alpha$  ( $P < 0.01$ ). Similarly, participants who consumed  $>360$  mg/d of betaine had, on average, 10% lower concentrations of homocysteine ( $P < 0.01$ ), 19% lower concentrations of C-reactive protein ( $P < 0.1$ ), and 12% lower concentrations of tumor necrosis factor- $\alpha$  ( $P < 0.05$ ) than did those who consumed  $<260$  mg/d. These findings were independent of various sociodemographic, lifestyle, and clinical characteristics of the participants.

#### CONCLUSIONS:

Our results support an association between choline and betaine intakes and the inflammation process in free-eating and apparently healthy adults. However, further studies are needed to confirm or refute our findings.

Source

Detopoulou P et al. Dietary choline and betaine intakes in relationship to concentrations of inflammatory markers in healthy adults: the ATTICA study. *Am J Clin Nutr* 2008;87:424-430.

#### A Multi-nutrient supplement reduced markers of inflammation and improved physical performance in active individuals of middle to older age: a randomized, double-blind, placebo-controlled study

#### ABSTRACT

##### BACKGROUND:

While exercise acts to combat inflammation and aging, the ability to exercise may itself be compromised by inflammation and inflammation's impact on muscle recovery and joint inflammation. A number of nutritional supplements have been shown to reduce inflammation and improve recovery. The purpose of the current investigation was to examine the effect of

a multi-nutrient supplement containing branched chain amino acids, taurine, anti-inflammatory plant extracts, and B vitamins on inflammatory status, endothelial function, physical function, and mood in middle-aged individuals.

#### METHODS:

Thirty-one healthy and active men ( $N = 16$ , mean age  $56 \pm 6.0$  yrs) and women ( $N = 15$ , mean age  $= 52 \pm 7.5$  yrs) participated in this investigation. Subjects completed one 28 day cycle of placebo supplementation and one 28 day cycle of multi-nutrient supplementation (separated by a one week washout period) in a balanced, randomized, double-blind, cross-over design. Subjects completed weekly perceptual logs (PROMIS-57, KOOS) and pre- and post- testing around the supplementation period. Testing consisted of brachial artery flow mediated dilation (FMD), blood measures, and physical performance on vertical jump, handgrip strength, and balance (dispersion from center of pressure). Significance for the investigation was  $p \leq 0.05$ .

#### RESULTS:

IL-6 significantly decreased in both men (from  $1.2 \pm 0.2$  to  $0.7 \pm 0.4$  pg-mL $^{-1}$ ) and women (from  $1.16 \pm 0.04$  to  $0.7 \pm 0.4$  pg-mL $^{-1}$ ). Perceived energy also improved for both men (placebo:  $1.8 \pm 0.7$ ; supplement:  $3.7 \pm 0.8$  AUC) and women (placebo:  $1.2 \pm 0.7$ ; supplement:  $2.8 \pm 0.8$  AUC). Alpha-1-antichymotrypsin (from  $108.9 \pm 38.6$  to  $55.5 \pm 22.2$  ug-mL $^{-1}$ ), Creatine Kinase (from  $96 \pm 34$  to  $67 \pm 23$  IU-L $^{-1}$ ), general pain, and joint pain decreased in men only, while anxiety and balance (from  $0.52 \pm 0.13$  to  $0.45 \pm 0.12$  cm) improved in women only. Men showed increased performance in vertical jump power (from  $2642 \pm 244$  to  $3134 \pm 282$  W) and grip strength (from  $42.1 \pm 5.9$  to  $48.5 \pm 4.9$  kg).

#### CONCLUSIONS:

A multi-nutrient supplement is effective in improving inflammatory status in both men and women, markers of pain, joint pain, strength, and power in men only, and both anxiety and balance (a risk factor for hip fracture) in women.



Therefore, a multi-nutrient supplement may help middle-aged individuals to prolong physical function and maintain a healthy, active lifestyle.

#### Source

Dunn-Lewis C et al. A Multi-nutrient supplement reduced markers of inflammation and improved physical performance in active individuals of middle to older age: a randomized, double-blind, placebo-controlled study. *Nutr J* 10:90, 2011.

### **Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease**

#### ABSTRACT

Most humans depend on sun exposure to satisfy their requirements for vitamin D. Solar ultraviolet B photons are absorbed by 7-dehydrocholesterol in the skin, leading to its transformation to previtamin D<sub>3</sub>, which is rapidly converted to vitamin D<sub>3</sub>. Season, latitude, time of day, skin pigmentation, aging, sunscreen use, and glass all influence the cutaneous production of vitamin D<sub>3</sub>. Once formed, vitamin D<sub>3</sub> is metabolized in the liver to 25-hydroxyvitamin D<sub>3</sub> and then in the kidney to its biologically active form, 1,25-dihydroxyvitamin D<sub>3</sub>. Vitamin D deficiency is an unrecognized epidemic among both children and adults in the United States. Vitamin D deficiency not only causes rickets among children but also precipitates and exacerbates osteoporosis among adults and causes the painful bone disease osteomalacia. Vitamin D deficiency has been associated with increased risks of deadly cancers, cardiovascular disease, multiple sclerosis, rheumatoid arthritis, and type 1 diabetes mellitus. Maintaining blood concentrations of 25-hydroxyvitamin D above 80 nmol/L (approximately 30 ng/mL) not only is important for maximizing intestinal calcium absorption but also may be important for providing the extrarenal 1 $\alpha$ -hydroxylase that is present in most tissues to produce 1,25-dihydroxyvitamin D<sub>3</sub>. Although chronic excessive exposure to sunlight increases the risk of nonmelanoma skin cancer,

the avoidance of all direct sun exposure increases the risk of vitamin D deficiency, which can have serious consequences. Monitoring serum 25-hydroxyvitamin D concentrations yearly should help reveal vitamin D deficiencies. Sensible sun exposure (usually 5-10 min of exposure of the arms and legs or the hands, arms, and face, 2 or 3 times per week) and increased dietary and supplemental vitamin D intakes are reasonable approaches to guarantee vitamin D sufficiency.

#### Source

Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *Am J Clin Nutr*. 2004 Dec;80(6 Suppl):1678S-88S.

### **Vitamin C status and perception of effort during exercise in obese adults adhering to a calorie-reduced diet**

#### ABSTRACT

##### **OBJECTIVE:**

Moderate energy restriction and exercise are recommended for effective weight loss. Obese individuals oxidize less fat and report a higher perceived exertion during exercise, characteristics that may negatively influence exercise behavior. Because vitamin C status has been linked to fatigability, we compared the effects of vitamin C supplementation on self-reported fatigue and on the respiratory exchange ratio and the Ratings of Perceived Exertion scale during moderate exercise in healthy obese adults adhering to a hypocaloric diet.

##### **METHODS:**

Twenty adults (4 men and 16 women) were stratified and randomly assigned to receive 500 mg of vitamin C (VC) or placebo (CON) daily for 4 wk while adhering to a vitamin C-controlled, calorie-restricted diet. Feelings of general fatigue as assessed by the Profile of Mood States questionnaire were recorded on a separate day from the exercise session at weeks 0 and 4. Participants walked on a treadmill at an intensity of 50% predicted maximal oxygen consumption for 60 min at weeks 0 and 4, and heart rate, respiratory exchange ratio,

and Ratings of Perceived Exertion were recorded.

After 4 wk, the two groups lost similar amounts of weight ( $\approx$  4 kg), and the respiratory exchange ratio was not altered by group. Heart rate and the Ratings of Perceived Exertion during exercise were significantly decreased in the VC versus the CON group (-11 versus -3 beats/min,  $P = 0.022$ , and -1.3 versus +0.1 U,  $P = 0.001$ , respectively), and the general fatigue score was decreased 5.9 U for the VC group versus a 1.9 U increase for the CON group ( $P = 0.001$ ).

#### CONCLUSION:

These data provide preliminary evidence that vitamin C status may influence fatigue, heart rate, and perceptions of exertion during moderate exercise in obese individuals.

#### Source

Huck CJ et al. Vitamin C status and perception of effort during exercise in obese adults adhering to a calorie-reduced diet. *Nutr* [Epub June 5, 2012].

### **Oral magnesium supplementation in adults with coronary heart disease or coronary heart disease risk**

#### ABSTRACT

##### **PURPOSE:**

To review randomized control clinical trial (RCT) literature and prospective studies for the safety and efficacy of magnesium supplements in patients with coronary heart disease (CHD) or with CHD risk.

##### **DATA SOURCES:**

Databases were searched using the keywords: magnesium, heart disease, endothelium, prevention, treatment, therapy, level, and supplement.

##### **CONCLUSIONS:**

There were no reports of adverse effects from magnesium supplementation in any of the studies. Subjects reporting lower dietary magnesium intake had significantly lower serum magnesium concentrations than those reporting higher dietary magnesium intake and,

in some cases, had a significantly higher frequency of supraventricular beats. There was a modest relationship between dietary magnesium intake and a reduced risk of CHD in male subjects; however, there was no noted decrease in the development of CHD disease in women who had high magnesium intake.

#### IMPLICATIONS FOR PRACTICE:

Magnesium is vital for many functions in the body and magnesium supplementation is safe. There is a possible association between a modestly lower risk of CHD in men and increased magnesium intake; therefore, it is reasonable to encourage diets high in magnesium as a potential means to lower the risk of CHD.

#### Source

Mathers TW, et al. Oral magnesium supplementation in adults with coronary heart disease or coronary heart disease risk. *J Am Acad Nurs Pract.* 2009 Dec; 21(12):651-7

#### Serum 25-Hydroxyvitamin D Levels and the Prevalence of Peripheral Arterial Disease. Results from NHANES 2001 to 2004

#### ABSTRACT

##### OBJECTIVE:

The purpose of this study was to determine the association between 25-hydroxyvitamin D (25(OH)D) levels and the prevalence of peripheral arterial disease (PAD) in the general United States population.

##### METHODS AND RESULTS:

We analyzed data from 4839 participants of the National Health and Nutrition Examination Survey 2001 to 2004 to evaluate the relationship between 25(OH)D and PAD (defined as an ankle-brachial index < 0.9). Across quartiles of 25(OH)D, from lowest to highest, the prevalence of PAD was 8.1%, 5.4%, 4.9%, and 3.7% (P trend < 0.001). After multivariable adjustment for demographics, comorbidities, physical activity level, and laboratory measures, the prevalence ratio of PAD for the lowest, compared to the highest, 25(OH)D quartile (< 17.8 and >

or = 29.2 ng/mL, respectively) was 1.80 (95% confidence interval: 1.19, 2.74). For each 10 ng/mL lower 25(OH)D level, the multivariable-adjusted prevalence ratio of PAD was 1.35 (95% confidence interval: 1.15, 1.59).

##### CONCLUSIONS:

Low serum 25(OH)D levels are associated with a higher prevalence of PAD. Several mechanisms have been invoked in the literature to support a potential antiatherosclerotic activity of vitamin D. Prospective cohort and mechanistic studies should be designed to confirm this association.

#### Source

Melamed ML, et al. Serum 25-Hydroxyvitamin D Levels and the Prevalence of Peripheral Arterial Disease. Results from NHANES 2001 to 2004. *Arterioscler. Thromb. Vasc. Biol.* 2008; 28 (6): 1179

#### Effects of vitamin D and calcium supplementation on pancreatic B cell function, insulin sensitivity, and glycemia in adults at high risk of diabetes: the Calcium and Vitamin D for Diabetes Mellitus (CaDDM) randomized controlled trial

#### ABSTRACT

##### BACKGROUND:

A suboptimal vitamin D and calcium status has been associated with higher risk of type 2 diabetes in observational studies, but evidence from trials is lacking.

##### OBJECTIVE:

We determined whether vitamin D supplementation, with or without calcium, improved glucose homeostasis in adults at high risk of diabetes.

##### DESIGN:

Ninety-two adults were randomly assigned in a 2-by-2 factorial-design, double-masked, placebo-controlled trial to receive either cholecalciferol (2000 IU once daily) or calcium carbonate (400 mg twice daily) for 16 wk. The primary outcome was the change in pancreatic  $\beta$  cell function as measured by the disposition index after an intravenous-glucose-tolerance test. Other

outcomes were acute insulin response, insulin sensitivity, and measures of glycemia.

##### RESULTS:

Participants had a mean age of 57 y, a body mass index (BMI; in kg/m<sup>2</sup>) of 32, and glycated hemoglobin (Hb A(1c)) of 5.9%. There was no significant vitamin D  $\times$  calcium interaction on any outcomes. The disposition index increased in the vitamin D group and decreased in the no-vitamin D group (adjusted mean change  $\pm$  SE: 300  $\pm$  130 compared with -126  $\pm$  127, respectively; P = 0.011), which was explained by an improvement in insulin secretion (62  $\pm$  39 compared with -36  $\pm$  37 mU  $\cdot$  L(-1)  $\cdot$  min, respectively; P = 0.046). Hb A(1c) increased less, but nonsignificantly, in the vitamin D group than in the no-vitamin D group (0.06  $\pm$  0.03% compared with 0.14  $\pm$  0.03%, respectively; P = 0.081). There was no significant difference in any outcomes with calcium compared with no calcium.

##### CONCLUSION:

In adults at risk of type 2 diabetes, short-term supplementation with cholecalciferol improved  $\beta$  cell function and had a marginal effect on attenuating the rise in Hb A(1c). This trial was registered at clinicaltrials.gov as NCT00436475.

#### Source

Mitri J et al. Effects of vitamin D and calcium supplementation on pancreatic B cell function, insulin sensitivity, and glycemia in adults at high risk of diabetes: the Calcium and Vitamin D for Diabetes Mellitus (CaDDM) randomized controlled trial. *Am J*

#### Relationship of serum and dietary magnesium to incident hypertension: the Atherosclerosis Risk in Communities (ARIC) Study

#### ABSTRACT

##### PURPOSE:

To examine the relationship of serum and dietary magnesium (Mg) with incident hypertension. The setting was the Atherosclerosis Risk in Communities

(ARIC) Study, which included a biracial cohort, aged 45-64 years, from four U.S. communities.

#### **METHODS:**

This analysis included 7731 participants (4190 women and 3541 men) free of hypertension at baseline and followed six years. Fasting serum Mg was measured, and usual dietary intake was assessed with a food frequency questionnaire.

#### **RESULTS:**

After adjustment for age, race, and a number of other risk factors, the odds of incident hypertension across ascending quartiles of serum Mg were 1.0, 0.79, 0.85, and 0.70 in women (p trend = 0.01) and 1.0, 0.87, 0.87, and 0.82 in men (p trend = 0.16). We found no association between dietary Mg intake and incident hypertension. These associations were attenuated after the addition of baseline systolic blood pressure to the models.

#### **CONCLUSIONS:**

This study suggests that low Mg may play a modest role in the development of hypertension.

#### **Source**

Peacock JM, et al. Relationship of serum and dietary magnesium to incident hypertension: the Atherosclerosis Risk in Communities (ARIC) Study. *Annals of Epidemiology* 1999;9:159-65.

#### **Multivitamin use and the risk of myocardial infarction: a population-based cohort of Swedish women**

#### **ABSTRACT**

##### **BACKGROUND:**

Dietary supplements are widely used in industrialized countries.

##### **OBJECTIVE:**

The objective was to examine the association between multivitamin use and myocardial infarction (MI) in a prospective, population-based cohort of women.

##### **DESIGN:**

The study included 31,671 women with no history of cardiovascular disease (CVD) and 2262 women with a history of CVD aged 49-83 y from Sweden. Women completed a self-administered questionnaire in 1997

regarding dietary supplement use, diet, and lifestyle factors. Multivitamins were estimated to contain nutrients close to recommended daily allowances: vitamin A (0.9 mg), vitamin C (60 mg), vitamin D (5 µg), vitamin E (9 mg), thiamine (1.2 mg), riboflavin (1.4 mg), vitamin B-6 (1.8 mg), vitamin B-12 (3 µg), and folic acid (400 µg).

##### **RESULTS:**

During an average of 10.2 y of follow-up, 932 MI cases were identified in the CVD-free group and 269 cases in the CVD group. In the CVD-free group, use of multivitamins only, compared with no use of supplements, was associated with a multivariable-adjusted hazard ratio (HR) of 0.73 (95% CI: 0.57, 0.93). The HR for multivitamin use together with other supplements was 0.70 (95% CI: 0.57, 0.87). The HR for use of supplements other than multivitamins was 0.93 (95% CI: 0.81, 1.08). The use of multivitamins for ≥5 y was associated with an HR of 0.59 (95% CI: 0.44, 0.80). In the CVD group, use of multivitamins alone or together with other supplements was not associated with MI.

##### **CONCLUSIONS:**

The use of multivitamins was inversely associated with MI, especially long-term use among women with no CVD. Further prospective studies with detailed information on the content of preparations and the duration of use are needed to confirm or refute our findings.

#### **Source**

Rautiainen S et al. Multivitamin use and the risk of myocardial infarction: a population-based cohort of Swedish women. *Am J Clin Nutr*. 95:1251-6, 2010.

#### **Calcium and vitamin D supplementation is associated with decreased abdominal visceral adipose tissue in overweight and obese adults**

#### **ABSTRACT**

##### **BACKGROUND:**

Several studies suggest that calcium and vitamin D (CaD) may play a role in the regulation of abdominal fat mass.

##### **OBJECTIVE:**

This study investigated the effect of CaD-supplemented orange juice (OJ) on weight loss and reduction of visceral adipose tissue (VAT) in overweight and obese adults (mean ± SD age: 40.0 ± 12.9 y).

##### **DESIGN:**

Two parallel, double-blind, placebo-controlled trials were conducted with either regular or reduced-energy (lite) orange juice. For each 16-wk trial, 171 participants were randomly assigned to 1 of 2 groups. The treatment groups consumed three 240-mL glasses of OJ (regular or lite) fortified with 350 mg Ca and 100 IU vitamin D per serving, and the control groups consumed either unfortified regular or lite OJ. Computed tomography scans of VAT and subcutaneous adipose tissue were performed by imaging a single cut at the lumbar 4 level.

##### **RESULTS:**

After 16 wk, the average weight loss (2.45 kg) did not differ significantly between groups. In the regular OJ trial, the reduction of VAT was significantly greater (P = 0.024) in the CaD group (-12.7 ± 25.0 cm(2)) than in the control group (-1.3 ± 13.6 cm(2)). In the lite OJ trial, the reduction of VAT was significantly greater (P = 0.039) in the CaD group (-13.1 ± 18.4 cm(2)) than in the control group (-6.4 ± 17.5 cm(2)) after control for baseline VAT. The effect of calcium and vitamin D on VAT remained highly significant when the results of the 2 trials were combined (P = 0.007).

##### **CONCLUSIONS:**

The findings suggest that calcium and/or vitamin D supplementation contributes to a beneficial reduction of VAT. This trial is registered at clinicaltrials.gov as NCT00386672, NCT01363115.

#### **Source**

Rosenblum JL et al. Calcium and vitamin D supplementation is associated with decreased abdominal visceral adipose tissue in overweight and obese adults. *Am J Clin Nutr* 95:101-8, 2011.

## MAGNESIUM.

### An update on physiological, clinical and analytical aspects

#### ABSTRACT

There is an increased interest in the role of magnesium ions in clinical medicine, nutrition and physiology. The characteristics of the binding of magnesium and calcium ions to various components, macromolecules and biological membranes are described. Magnesium affects many cellular functions, including transport of potassium and calcium ions, and modulates signal transduction, energy metabolism and cell proliferation. The mechanism of cellular uptake and efflux of magnesium, its intracellular transport, intestinal absorption, renal excretion and the effect of hormones on these are reviewed. Magnesium deficiency is not uncommon among the general population: its intake has decreased over the years especially in the western world. The magnesium supplementation or intravenous infusion may be beneficial in various diseased states. Of special interest is the magnesium status in alcoholism, eclampsia, hypertension, atherosclerosis, cardiac diseases, diabetes, and asthma. The development of instrumentation for the assay of ionized magnesium is reviewed, as are the analytical procedures for total magnesium in blood and free magnesium in the cytosol. The improved procedures for the assay of different magnesium states are useful in understanding the role of magnesium in health and disease.

#### Source

Saris NE, et al. Magnesium. An update on physiological, clinical and analytical aspects. Clin Chim Acta. 2000 Apr; 294(1-2):1-26.

### The effect of nutrition on blood pressure

#### ABSTRACT

The incidence and severity of hypertension are affected by nutritional status and intake of many nutrients. Excessive energy intake and obesity are major causes of

hypertension. Obesity is associated with increased activity of the renin-angiotensin-aldosterone and sympathetic nervous systems, possibly other mineralcorticoid activity, insulin resistance, salt-sensitive hypertension and excess salt intake, and reduced kidney function. High sodium chloride intake strongly predisposes to hypertension. Increased alcohol consumption may acutely elevate blood pressure. High intakes of potassium, polyunsaturated fatty acids, and protein, along with exercise and possibly vitamin D, may reduce blood pressure. Less-conclusive studies suggest that amino acids, tea, green coffee bean extract, dark chocolate, and foods high in nitrates may reduce blood pressure. Short-term studies indicate that specialized diets may prevent or ameliorate mild hypertension; most notable are the Dietary Approaches to Stop Hypertension (DASH) diet, which is high in fruits, vegetables, and low-fat dairy products, and the DASH low-sodium diet. Long-term compliance to these diets remains a major concern.

#### Source

Savica V et al. The effect of nutrition on blood pressure. Annu Rev Nutr 30:365-401, 2010.

## IMMUNE HEALTH

### Recent advances in clinical research involving carotenoids

#### ABSTRACT

Epidemiological studies show consistent decreased risk of lung cancer and certain other cancers, cataracts, age-related macular degeneration, and coronary heart disease in populations with the highest intakes of carotenoid-rich diets. Intervention studies show reductions in precancerous oral lesions, enhancement in immune parameters, and reduced incidence of cardiovascular events in individuals supplemented with  $\beta$ -carotene.

#### Source

Bendich A, et al. Recent advances in

clinical research involving carotenoids. Pure & Appl Chem. 1994;66(5): 1017-1024.

### Physicians and nurses use and recommend dietary supplements: report of a survey

#### ABSTRACT

##### BACKGROUND:

Homocysteine is a risk factor for Alzheimer's disease. In the first report on the VITACOG trial, we showed that homocysteine-lowering treatment with B vitamins slows the rate of brain atrophy in mild cognitive impairment (MCI). Here we report the effect of B vitamins on cognitive and clinical decline (secondary outcomes) in the same study.

##### METHODS:

This was a double-blind, single-centre study, which included participants with MCI, aged  $\geq 70$  y, randomly assigned to receive a daily dose of 0.8 mg folic acid, 0.5 mg vitamin B(12) and 20 mg vitamin B(6) (133 participants) or placebo (133 participants) for 2 y. Changes in cognitive or clinical function were analysed by generalized linear models or mixed-effects models.

##### RESULTS:

The mean plasma total homocysteine was 30% lower in those treated with B vitamins relative to placebo. B vitamins stabilized executive function (CLOX) relative to placebo ( $P = 0.015$ ). There was significant benefit of B-vitamin treatment among participants with baseline homocysteine above the median (11.3  $\mu\text{mol/L}$ ) in global cognition (Mini Mental State Examination,  $P < 0.001$ ), episodic memory (Hopkins Verbal Learning Test-delayed recall,  $P = 0.001$ ) and semantic memory (category fluency,  $P = 0.037$ ). Clinical benefit occurred in the B-vitamin group for those in the upper quartile of homocysteine at baseline in global clinical dementia rating score ( $P = 0.02$ ) and IQCODE score ( $P = 0.01$ ).

##### CONCLUSION:

In this small intervention trial, B vitamins appear to slow cognitive and clinical decline in people with MCI, in particular in those with elevated homocysteine.



Further trials are needed to see if this treatment will slow or prevent conversion from MCI to dementia.

#### Source

Dickinson A, et al. Physicians and nurses use and recommend dietary supplements: report of a survey. *Nutr J.* 2009 Jul 1;8:29.

#### **Effect of low carotene diet on malondialdehyde (MDA) concentration**

**\*Note: This study does not apply to Formula IV Plus.**

#### ABSTRACT

##### **OBJECTIVE:**

The purpose of the study was to evaluate the effect of a low carotenoid diet (83 micrograms Beta-carotene) on malondialdehyde-thiobarbituric acid (MDA-TBA) concentrations of nine pre-menopausal women.

##### **METHODS:**

Subjects lived on the metabolic research unit of the Western Human Nutrition Research Center (WHNRC), where diet, exercise and other activities were controlled. Five subjects (Group C, control group) consumed a low carotenoid diet and received an additional 0.5 mg/day of Beta-carotene while four subjects (Group P, placebo group) received only the low carotenoid diet during days 1 to 60 (period 1). All subjects received 0.5 mg/day of Beta-carotene during days 60 to 100 (period 2), plus three capsules/day mixed carotenoid supplement (Neo-Life Company) during study days 100 to 120. Changes in MDA-TBA concentrations were analyzed during the study periods and between the groups.

##### **RESULTS:**

At the start of the study (day 1), no significant difference in the MDA-TBA concentration was observed between the control (Group C) and the placebo (Group P) subjects. During period 1 (days 2 to 60), when Group P subjects consumed the low carotenoid diet without supplementation, the MDA-TBA values for Group P rose markedly and were significantly ( $p < 0.05$ ) higher than the MDA-TBA values for Group C subjects who were receiving carotenoid

supplementation. During period 2 (days 60 to 100) when both groups received carotenoid supplementation, the MDA-TBA values of Group P subjects were significantly ( $p < 0.05$ ) reduced to the point where they were similar to the MDA-TBA values for Group C subjects.

##### **CONCLUSIONS:**

These findings provide evidence to support the beneficial effects of carotenoids in preventing lipid peroxidation in the cells. Further studies are needed to identify the exact mechanism by which carotenoids prevent lipid peroxidation and the amount needed for normal activity.

#### Source

Dixon ZR, et al. Effect of low carotene diet on malondialdehyde (MDA) concentration; *Free Radic Biol Med.* 1996.

#### **Effects of a carotene-deficient diet on measures of oxidative susceptibility and superoxide dismutase activity in adult women**

**\*Note: This study does not apply to Formula IV Plus.**

#### ABSTRACT

The effect of consuming a low carotene diet (approximately 60 micrograms carotene/day) on oxidative susceptibility and superoxide dismutase (SOD) activity in women living in a metabolic research unit was evaluated. The diet had sufficient vitamins A, E, and C. The women ate the diet supplemented with 1500 micrograms/day beta-carotene for 4 days (baseline), then the unsupplemented diet for 68 days (depletion), followed by the diet supplemented with > 15,000 micrograms/day carotene for 28 days (repletion). Production of hexanal, pentanal, and pentane by copper-oxidized plasma low density lipoproteins from carotene-depleted women was greater than their production of these compounds when repleted with carotene. Erythrocyte SOD activity was depressed in carotene-depleted women; it recovered with repletion. Thiobarbituric acid reactive substances in plasma of carotene-depleted women were elevated and diminished with repletion. Dietary carotene seems to be needed, not only

as a precursor of vitamin A, but also to inhibit oxidative damage and decrease oxidation susceptibility.

#### Source

Dixon ZR, et al. Effects of a carotene-deficient diet on measures of oxidative susceptibility and superoxide dismutase activity in adult women. *Free Radic Biol Med.* 1994 Dec;17(6):537-44.

#### **Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease**

#### ABSTRACT

Most humans depend on sun exposure to satisfy their requirements for vitamin D. Solar ultraviolet B photons are absorbed by 7-dehydrocholesterol in the skin, leading to its transformation to previtamin D3, which is rapidly converted to vitamin D3. Season, latitude, time of day, skin pigmentation, aging, sunscreen use, and glass all influence the cutaneous production of vitamin D3. Once formed, vitamin D3 is metabolized in the liver to 25-hydroxyvitamin D3 and then in the kidney to its biologically active form, 1,25-dihydroxyvitamin D3. Vitamin D deficiency is an unrecognized epidemic among both children and adults in the United States. Vitamin D deficiency not only causes rickets among children but also precipitates and exacerbates osteoporosis among adults and causes the painful bone disease osteomalacia. Vitamin D deficiency has been associated with increased risks of deadly cancers, cardiovascular disease, multiple sclerosis, rheumatoid arthritis, and type 1 diabetes mellitus. Maintaining blood concentrations of 25-hydroxyvitamin D above 80 nmol/L (approximately 30 ng/mL) not only is important for maximizing intestinal calcium absorption but also may be important for providing the extrarenal 1 $\alpha$ -hydroxylase that is present in most tissues to produce 1,25-dihydroxyvitamin D3. Although chronic excessive exposure to sunlight increases the risk of nonmelanoma skin cancer, the

avoidance of all direct sun exposure increases the risk of vitamin D deficiency, which can have serious consequences. Monitoring serum 25-hydroxyvitamin D concentrations yearly should help reveal vitamin D deficiencies. Sensible sun exposure (usually 5-10 min of exposure of the arms and legs or the hands, arms, and face, 2 or 3 times per week) and increased dietary and supplemental vitamin D intakes are reasonable approaches to guarantee vitamin D sufficiency.

#### Source

Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *Am J Clin Nutr.* 2004 Dec;80(6 Suppl):1678S-88S.

#### **Modulated mitogenic proliferative responsiveness of lymphocytes in whole-blood cultures after a low-carotene diet and mixed-carotenoid supplementation in women**

**\*Note: This study does not apply to Formula IV Plus.**

#### ABSTRACT

To determine the effects of dietary carotenes on the mitogenic proliferative responsiveness of blood lymphocytes in vitro, nine premenopausal women were fed a low-carotene diet for 120 d. Low-dose beta-carotene (0.5 mg/d) was given to five subjects on days 1-60, while four received a placebo. All subjects received a low-dose beta-carotene (0.5 mg/d) supplement on days 61-120, plus a carotenoid complex on days 101-120. The mean ( $\pm$ SEM) serum beta-carotene concentration for the combined beta-carotene supplemented and placebo subjects ( $n = 9$ ) was not significantly reduced from that on day 1 ( $1.27 \pm 0.24$   $\mu$ mol/L) on days 60 ( $0.66 \pm 0.14$   $\mu$ mol/L) and 100 ( $0.91 \pm 0.38$   $\mu$ mol/L), but on day 120 ( $3.39 \pm 0.44$   $\mu$ mol/L) it was increased above that on days 1, 60, and 100. Maximum mitogenic proliferative responsiveness of blood lymphocytes in vitro to optimal dose phytohemagglutinin (PHA) was reduced on days 60 ( $P = 0.025$ ) and 100 ( $P <$

0.0001), but corrected itself on day 120 to a value above those on day 1 ( $P = 0.04$ ), day 60 ( $P = 0.0001$ ), and day 100 ( $P < 0.0001$ ). Present findings show that a diet low in carotene had a suppressive effect on the maximum mitogenic proliferative responsiveness of blood lymphocytes in vitro, which was not corrected with low-dose beta-carotene supplementation but was with a carotenoid complex from vegetables rich in carotenoids.

#### Source

Kramer TR, et al. Modulated mitogenic proliferative responsiveness of lymphocytes in whole-blood cultures after a low-carotene diet and mixed-carotenoid supplementation in women. *Am J Clin Nutr.* 1997 Mar;65(3):871-5.

Effects of vitamin D and calcium supplementation on pancreatic B cell function, insulin sensitivity, and glycemia in adults at high risk of diabetes: the Calcium and Vitamin D for Diabetes Mellitus (CaDDM) randomized controlled trial

#### ABSTRACT

##### **BACKGROUND:**

A suboptimal vitamin D and calcium status has been associated with higher risk of type 2 diabetes in observational studies, but evidence from trials is lacking.

##### **OBJECTIVE:**

We determined whether vitamin D supplementation, with or without calcium, improved glucose homeostasis in adults at high risk of diabetes.

##### **DESIGN:**

Ninety-two adults were randomly assigned in a 2-by-2 factorial-design, double-masked, placebo-controlled trial to receive either cholecalciferol (2000 IU once daily) or calcium carbonate (400 mg twice daily) for 16 wk. The primary outcome was the change in pancreatic  $\beta$  cell function as measured by the disposition index after an intravenous-glucose-tolerance test. Other outcomes were acute insulin response, insulin sensitivity, and measures of glycemia.

##### **RESULTS:**

Participants had a mean age of 57 y, a

body mass index (BMI; in  $\text{kg}/\text{m}^2$ ) of 32, and glycated hemoglobin (Hb A(1c)) of 5.9%. There was no significant vitamin D  $\times$  calcium interaction on any outcomes. The disposition index increased in the vitamin D group and decreased in the no-vitamin D group (adjusted mean change  $\pm$  SE:  $300 \pm 130$  compared with  $-126 \pm 127$ , respectively;  $P = 0.011$ ), which was explained by an improvement in insulin secretion ( $62 \pm 39$  compared with  $-36 \pm 37$   $\text{mU} \cdot \text{L}^{-1} \cdot \text{min}$ , respectively;  $P = 0.046$ ). Hb A(1c) increased less, but nonsignificantly, in the vitamin D group than in the no-vitamin D group ( $0.06 \pm 0.03\%$  compared with  $0.14 \pm 0.03\%$ , respectively;  $P = 0.081$ ). There was no significant difference in any outcomes with calcium compared with no calcium.

##### **CONCLUSION:**

In adults at risk of type 2 diabetes, short-term supplementation with cholecalciferol improved  $\beta$  cell function and had a marginal effect on attenuating the rise in Hb A(1c). This trial was registered at clinicaltrials.gov as NCT00436475.

#### Source

Mitri J et al. Effects of vitamin D and calcium supplementation on pancreatic B cell function, insulin sensitivity, and glycemia in adults at high risk of diabetes: the Calcium and Vitamin D for Diabetes Mellitus (CaDDM) randomized controlled trial. *Am J*

#### **Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis**

#### ABSTRACT

##### **CONTEXT:**

Epidemiological and experimental evidence suggests that high levels of vitamin D, a potent immunomodulator, may decrease the risk of multiple sclerosis. There are no prospective studies addressing this hypothesis.

##### **OBJECTIVE:**

To examine whether levels of 25-hydroxyvitamin D are associated with risk of multiple sclerosis.

##### **DESIGN, SETTING, AND**

## PARTICIPANTS:

Prospective, nested case-control study among more than 7 million US military personnel who have serum samples stored in the Department of Defense Serum Repository. Multiple sclerosis cases were identified through Army and Navy physical disability databases for 1992 through 2004, and diagnoses were confirmed by medical record review. Each case (n = 257) was matched to 2 controls by age, sex, race/ethnicity, and dates of blood collection. Vitamin D status was estimated by averaging 25-hydroxyvitamin D levels of 2 or more serum samples collected before the date of initial multiple sclerosis symptoms.

## MAIN OUTCOME MEASURES:

Odds ratios of multiple sclerosis associated with continuous or categorical levels (quantiles or a priori-defined categories) of serum 25-hydroxyvitamin D within each racial/ethnic group.

## RESULTS:

Among whites (148 cases, 296 controls), the risk of multiple sclerosis significantly decreased with increasing levels of 25-hydroxyvitamin D (odds ratio [OR] for a 50-nmol/L increase in 25-hydroxyvitamin D, 0.59; 95% confidence interval, 0.36-0.97). In categorical analyses using the lowest quintile (<63.3 nmol/L) as the reference, the ORs for each subsequent quintile were 0.57, 0.57, 0.74, and 0.38 (P = .02 for trend across quintiles). Only the OR for the highest quintile, corresponding to 25-hydroxyvitamin D levels higher than 99.1 nmol/L, was significantly different from 1.00 (OR, 0.38; 95% confidence interval, 0.19-0.75; P = .006). The inverse relation with multiple sclerosis risk was particularly strong for 25-hydroxyvitamin D levels measured before age 20 years. Among blacks and Hispanics (109 cases, 218 controls), who had lower 25-hydroxyvitamin D levels than whites, no significant associations between vitamin D and multiple sclerosis risk were found.

## CONCLUSION:

The results of our study suggest that high circulating levels of vitamin D are associated with a lower risk of multiple sclerosis.

## Source

Munger KL, et al. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. JAMA. 2006 Dec 20;296(23):2832-8.

## Vitamin D controls T cell antigen receptor signaling and activation of human T cells

## ABSTRACT

Phospholipase C (PLC) isozymes are key signaling proteins downstream of many extracellular stimuli. Here we show that naive human T cells had very low expression of PLC-gamma1 and that this correlated with low T cell antigen receptor (TCR) responsiveness in naive T cells. However, TCR triggering led to an upregulation of approximately 75-fold in PLC-gamma1 expression, which correlated with greater TCR responsiveness. Induction of PLC-gamma1 was dependent on vitamin D and expression of the vitamin D receptor (VDR). Naive T cells did not express VDR, but VDR expression was induced by TCR signaling via the alternative mitogen-activated protein kinase p38 pathway. Thus, initial TCR signaling via p38 leads to successive induction of VDR and PLC-gamma1, which are required for subsequent classical TCR signaling and T cell activation.

## Source

von Essen MR, et al. Vitamin D controls T cell antigen receptor signaling and activation of human T cells. Nat Immunol. 2010 Apr;11(4):344-9.

## Update: effects of antioxidant and non-antioxidant vitamin supplementation on immune function

## ABSTRACT

The purpose of this manuscript is to review the impact of supplementation with vitamins E and C, carotenoids, and the B vitamins on parameters of innate and adaptive immune function as reported from clinical trials in humans. There is evidence to support causal effects of supplementation

with vitamins E and C and the carotenoids singly and in combination on selected aspects of immunity, including the functional capacity of innate immune cells, lymphocyte proliferation, and the delayed-type hypersensitivity (DTH) response. Controlled intervention trials of B vitamin-containing multivitamin supplements suggest beneficial effects on immune parameters and clinical outcomes in HIV-positive individuals.

## Source

Webb AL, et al. Update: effects of antioxidant and non-antioxidant vitamin supplementation on immune function. Nutr Rev. 2007 May;65(5):181-217.

## MEN'S HEALTH

## Effects of high-dose B vitamin complex with vitamin C and minerals on subjective mood and performance in healthy males

## ABSTRACT

### RATIONALE:

A significant proportion of the general population report supplementing their diet with one or more vitamins or minerals, with common reasons for doing so being to combat stress and fatigue and to improve mental functioning. Few studies have assessed the relationship between supplementation with vitamins/minerals and psychological functioning in healthy cohorts of non-elderly adults.

### OBJECTIVES:

The present randomised, placebo-controlled, double-blind, parallel groups trial assessed the cognitive and mood effects of a high-dose B-complex vitamin and mineral supplement (Berocca®) in 215 males aged 30 to 55 years, who were in full-time employment.

### METHODS:

Participants attended the laboratory prior to and on the last day of a 33-day treatment period where they completed the Profile of Mood States (POMS), Perceived Stress Scale (PSS) and General Health Questionnaire (GHQ-12). Cognitive

performance and task-related modulation of mood/fatigue were assessed with the 60 min cognitive demand battery. On the final day, participants also completed the Stroop task for 40 min whilst engaged in inclined treadmill walking and subsequent executive function was assessed.

#### RESULTS:

Vitamin/mineral supplementation led to significant improvements in ratings on the PSS, GHQ-12 and the 'vigour' subscale of the POMS. The vitamin/mineral group also performed better on the Serial 3s subtractions task and rated themselves as less 'mentally tired' both pre- and post-completion of the cognitive demand battery.

#### CONCLUSIONS:

Healthy members of the general population may benefit from augmented levels of vitamins/minerals via direct dietary supplementation. Specifically, supplementation led to improved ratings of stress, mental health and vigour and improved cognitive performance during intense mental processing.

Source

Kennedy DO et al. Effects of high-dose B vitamin complex with vitamin C and minerals on subjective mood and performance in healthy males. *Psychopharmacol* 211:55-68, 2010.

#### Oral magnesium supplementation in adults with coronary heart disease or coronary heart disease risk

#### ABSTRACT

##### PURPOSE:

To review randomized control clinical trial (RCT) literature and prospective studies for the safety and efficacy of magnesium supplements in patients with coronary heart disease (CHD) or with CHD risk.

##### DATA SOURCES:

Databases were searched using the keywords: magnesium, heart disease, endothelium, prevention, treatment, therapy, level, and supplement.

##### CONCLUSIONS:

There were no reports of adverse effects from magnesium supplementation in any

of the studies. Subjects reporting lower dietary magnesium intake had significantly lower serum magnesium concentrations than those reporting higher dietary magnesium intake and, in some cases, had a significantly higher frequency of supraventricular beats. There was a modest relationship between dietary magnesium intake and a reduced risk of CHD in male subjects; however, there was no noted decrease in the development of CHD disease in women who had high magnesium intake.

#### IMPLICATIONS FOR PRACTICE:

Magnesium is vital for many functions in the body and magnesium supplementation is safe. There is a possible association between a modestly lower risk of CHD in men and increased magnesium intake; therefore, it is reasonable to encourage diets high in magnesium as a potential means to lower the risk of CHD.

Source

Mathers TW, et al. Oral magnesium supplementation in adults with coronary heart disease or coronary heart disease risk. *J Am Acad Nurs Pract.* 2009 Dec; 21(12):651-7

#### The association of folate, zinc and antioxidant intake with sperm aneuploidy in healthy non-smoking men

#### ABSTRACT

##### BACKGROUND:

Little is known about the effect of paternal nutrition on aneuploidy in sperm. We investigated the association of normal dietary and supplement intake of folate, zinc and antioxidants (vitamin C, vitamin E and beta-carotene) with the frequency of aneuploidy in human sperm.

##### METHODS:

Sperm samples from 89 healthy, non-smoking men from a non-clinical setting were analysed for aneuploidy using fluorescent in situ hybridization with probes for chromosomes X, Y and 21. Daily total intake (diet and supplements) for zinc, folate, vitamin C, vitamin E and beta-carotene was derived from a food frequency questionnaire. Potential

confounders were obtained from a self-administered questionnaire.

#### RESULTS:

After adjusting for covariates, men with high folate intake (>75th percentile) had lower frequencies of sperm with disomies X, 21, sex nullisomy, and a lower aggregate measure of sperm aneuploidy ( $P \leq 0.04$ ) compared with men with lower intake. In adjusted continuous analyses, total folate intake was inversely associated with aggregate sperm aneuploidy (-3.6% change/100 microg folate; 95% CI: -6.3, -0.8) and results were similar for disomies X, 21 and sex nullisomy. No consistent associations were found between antioxidant or zinc intakes and sperm aneuploidy.

#### CONCLUSIONS:

Men with high folate intake had lower overall frequencies of several types of aneuploid sperm.

Source

Young SS, et al. The association of folate, zinc and antioxidant intake with sperm aneuploidy in healthy non-smoking men. *Human Reprod Epub* Mar 19, 2008.

#### OVARIAN HEALTH

#### The role of vitamin D in cancer prevention

#### ABSTRACT

Vitamin D status differs by latitude and race, with residents of the northeastern United States and individuals with more skin pigmentation being at increased risk of deficiency. A PubMed database search yielded 63 observational studies of vitamin D status in relation to cancer risk, including 30 of colon, 13 of breast, 26 of prostate, and 7 of ovarian cancer, and several that assessed the association of vitamin D receptor genotype with cancer risk. The majority of studies found a protective relationship between sufficient vitamin D status and lower risk of cancer. The evidence suggests that efforts to improve vitamin D status, for example by vitamin D supplementation, could reduce



cancer incidence and mortality at low cost, with few or no adverse effects.

#### Source

Garland CF, et al. The role of vitamin D in cancer prevention. Am J Public Health. 2006 Feb;96(2):252-61.

## PROSTATE HEALTH

### The promiscuous receptor

#### ABSTRACT

##### OBJECTIVE:

To determine the effectiveness of vitamin D therapy in patients with asymptomatic, prostate-specific antigen (PSA)-progression of prostate cancer.

##### PATIENTS AND METHODS:

Twenty-six patients with locally advanced or metastatic prostate cancer were treated with vitamin D. Vitamin D therapy was discontinued on disease progression as assessed by symptoms or serum PSA increase. The response to therapy was judged from changes in PSA level from the pretreatment baseline to 3 months after starting vitamin D therapy.

##### RESULTS:

Of the 26 patients, five (20%) responded to vitamin D; the mean (range) reduction in PSA level was 45.3 (15.9-95.1)%, and mean duration of response was 4-5 months. Patients in whom the PSA level was stabilized, but not reduced, after vitamin D treatment had a duration of response of up to 36 months. Treatment was well tolerated and was not associated with elevation of serum calcium levels. There was no significant correlation between response to therapy and stage of disease, Gleason grade, previous treatments or PSA level at diagnosis or initiation of vitamin D therapy.

##### CONCLUSION:

Vitamin D therapy is an effective and well tolerated treatment for patients with asymptomatic progressive prostate cancer, and is a useful addition to the therapeutic options.

#### Source

Newsom-Davis TE, et al. The promiscuous

receptor. BJU Int. 2009 Nov;104(9):1204-7

## SKIN HEALTH

### Vitamin D2 is as effective as vitamin D3 in maintaining circulating concentrations of 25-hydroxyvitamin D

#### ABSTRACT

##### CONTEXT:

Two reports suggested that vitamin D2 is less effective than vitamin D3 in maintaining vitamin D status.

##### OBJECTIVE:

Our objective was to determine whether vitamin D2 was less effective than vitamin D3 in maintaining serum 25-hydroxyvitamin D levels or increased the catabolism of 25-hydroxyvitamin D3.

##### SUBJECTS AND DESIGN:

This was a randomized, placebo-controlled, double-blinded study of healthy adults ages 18-84 yr who received placebo, 1000 IU vitamin D3, 1000 IU vitamin D2, or 500 IU vitamin D2 plus 500 IU vitamin D3 daily for 11 wk at the end of the winter.

##### RESULTS:

Sixty percent of the healthy adults were vitamin D deficient at the start of the study. The circulating levels of 25-hydroxyvitamin D (mean $\pm$ -sd) increased to the same extent in the groups that received 1000 IU daily as vitamin D2 (baseline 16.9 $\pm$ -10.5 ng/ml; 11 wk 26.8 $\pm$ -9.6 ng/ml), vitamin D3 (baseline 19.6 $\pm$ -11.1 ng/ml; 11 wk 28.9 $\pm$ -11.0 ng/ml), or a combination of 500 IU vitamin D2 and 500 IU vitamin D3 (baseline 20.2 $\pm$ -10.4 ng/ml; 11 wk 28.4 $\pm$ -7.7 ng/ml). The 25-hydroxyvitamin D3 levels did not change in the group that received 1000 IU vitamin D2 daily. The 1000 IU dose of vitamin D2 or vitamin D3 did not raise 25-hydroxyvitamin D levels in vitamin D-deficient subjects above 30 ng/ml.

##### CONCLUSION:

A 1000 IU dose of vitamin D2 daily was as effective as 1000 IU vitamin D3 in maintaining serum 25-hydroxyvitamin D levels and did not negatively influence serum 25-hydroxyvitamin D3 levels. Therefore, vitamin D2 is equally as effective as vitamin D3 in maintaining 25-hydroxyvitamin D status.

#### Source

Holick MF, et al. Vitamin D2 is as effective as vitamin D3 in maintaining circulating concentrations of 25-hydroxyvitamin D. J Clin Endocrinol Metab. 2008 Mar; 93(3):677-81.

### UVB photoprotection with antioxidants: effects of oral therapy with d-alpha-tocopherol and ascorbic acid on the minimal erythema dose

#### ABSTRACT

Ultraviolet radiation absorption is responsible for the production of free radicals in damaged cells. This side effect may be neutralized using antioxidant substances. It has been reported that ascorbic acid and d-alpha-tocopherol scavenge reactive oxygen species. In a single-blind controlled clinical trial we studied 45 healthy volunteers divided into three groups. Group 1 received d-alpha-tocopherol 1,200 I.U. daily; Group 2 ascorbic acid 2 g daily and Group 3 ascorbic acid 2 g plus d-alpha-tocopherol 1,200 I.U. daily. Treatment was sustained for one week. Before and after treatment, the minimal erythema dose was determined in all participants. The results show that the median minimal erythema dose increased from 60 to 65 mJ/cm<sup>2</sup> in Group 1 and from 50 to 70 mJ/cm<sup>2</sup> in Group 3. No modifications were observed in Group 2. We conclude that d-alpha-tocopherol prescribed in combination with ascorbic acid produces the best photoprotective effect.

#### Source

Mireles-Rocha H, et al. UVB photoprotection with antioxidants: effects of oral therapy with d-alpha-tocopherol and ascorbic acid on the minimal erythema dose. Acta Derm Venereol 82:21-4, 2002.

## Randomized controlled trial of oral omega-3 PUFA in solar-simulated radiation-induced suppression of human cutaneous immune responses

### ABSTRACT

#### BACKGROUND:

Skin cancer is a major public health concern, and the majority of cases are caused by solar ultraviolet radiation (UVR) exposure, which suppresses skin immunity. Omega-3 (n23) PUFAs protect against photoimmunosuppression and skin cancer in mice, but the impact in humans is unknown.

#### OBJECTIVES:

We hypothesized that EPA-rich n23 PUFA would abrogate photoimmunosuppression in humans. Therefore, a nutritional study was performed to assess the effect on UVR suppression of cutaneous cell-mediated immunity (CMI) reflected by nickel contact hypersensitivity (CHS).

#### DESIGN:

In a double-blind, randomized controlled study, 79 volunteers (nickel-allergic women, 22–60 y old, with phototype I or II) took 5 g n23 PUFA-containing lipid (70% EPA plus 10% DHA) or a control lipid daily for 3 mo. After supplementation, nickel was applied to 3 skin sites preexposed on 3 consecutive days to 1.9, 3.8, or 7.6 J/cm<sup>2</sup> of solar-simulated radiation (SSR) and to 3 unexposed control sites. Nickel CHS responses were quantified after 72 h and the percentage of immunosuppression by SSR was calculated. Erythrocyte [red blood cell (RBC)] EPA was measured by using gas chromatography.

#### RESULTS:

SSR dose-related suppression of the nickel CHS response was observed in both groups. Photoimmunosuppression appeared less in the n23 PUFA group than in the control group (not statistically significant [mean difference (95% CI): 6.9% (22.1%, 15.9%)]). The difference was greatest at 3.8 J/cm<sup>2</sup> SSR [mean difference: 11% (95% CI: 0.5%, 21.4%)]. Postsupplementation RBC EPA was 4-fold higher in the n23 PUFA group than in the control group (mean difference: 2.69% (95% CI: 2.23%, 3.14%), which confirmed the EPA bioavailability.

### CONCLUSION:

Oral n23 PUFAs appear to abrogate photoimmunosuppression in human skin, providing additional support for their chemopreventive role; verification of study findings is required. This trial was registered at clinicaltrials.gov as NCT01032343.

#### Source

Pilkington SM et al. Randomized controlled trial of oral omega-3 PUFA in solar-simulated radiation-induced suppression of human cutaneous immune responses. *Am J Clin Nutr* 97:646-52, 2013.

## Multivitamin use and the risk of myocardial infarction: a population-based cohort of Swedish women

### ABSTRACT

#### BACKGROUND:

Dietary supplements are widely used in industrialized countries.

#### OBJECTIVE:

The objective was to examine the association between multivitamin use and myocardial infarction (MI) in a prospective, population-based cohort of women.

#### DESIGN:

The study included 31,671 women with no history of cardiovascular disease (CVD) and 2262 women with a history of CVD aged 49–83 y from Sweden. Women completed a self-administered questionnaire in 1997 regarding dietary supplement use, diet, and lifestyle factors. Multivitamins were estimated to contain nutrients close to recommended daily allowances: vitamin A (0.9 mg), vitamin C (60 mg), vitamin D (5 µg), vitamin E (9 mg), thiamine (1.2 mg), riboflavin (1.4 mg), vitamin B-6 (1.8 mg), vitamin B-12 (3 µg), and folic acid (400 µg).

#### RESULTS:

During an average of 10.2 y of follow-up, 932 MI cases were identified in the CVD-free group and 269 cases in the CVD group. In the CVD-free group, use of multivitamins only, compared with no use of supplements, was associated with a multivariable-adjusted hazard ratio (HR) of 0.73 (95% CI: 0.57, 0.93). The HR for multivitamin use together with other

supplements was 0.70 (95% CI: 0.57, 0.87). The HR for use of supplements other than multivitamins was 0.93 (95% CI: 0.81, 1.08). The use of multivitamins for ≥5 y was associated with an HR of 0.59 (95% CI: 0.44, 0.80). In the CVD group, use of multivitamins alone or together with other supplements was not associated with MI.

### CONCLUSIONS:

The use of multivitamins was inversely associated with MI, especially long-term use among women with no CVD. Further prospective studies with detailed information on the content of preparations and the duration of use are needed to confirm or refute our findings.

#### Source

Rautiainen S et al. Multivitamin use and the risk of myocardial infarction: a population-based cohort of Swedish women. *Am J Clin Nutr*. 95:1251-6, 2010.

## Unraveling hidden secrets: The role of vitamin D in skin aging

### ABSTRACT

The skin is the only tissue in the human body that represents both a target tissue for biologically active vitamin D compounds including 1,25-dihydroxyvitamin D [1,25(OH)<sub>2</sub>D] and has the capacity for the synthesis of 1,25(OH)<sub>2</sub>D from 7-dehydrocholesterol (7-DHC). Recent findings indicate that the vitamin D endocrine system (VDES), besides multiple other important functions, regulates aging in many tissues, including skin. This concept is strongly supported by several independent studies in genetically modified mice (including FGF23<sup>-/-</sup> and Klotho<sup>-/-</sup> mice) that are characterized by altered mineral homeostasis caused by a high vitamin D activity. These mice typically have phenotypic features of premature aging that include, besides short lifespan, retarded growth, ectopic calcification, immunological deficiency, osteoporosis, atherosclerosis, hypogonadism, skin and general organ atrophy. Notably, it has been

demonstrated that these phenotypic features can be reversed by normalizing mineral homeostasis and/or vitamin D status. Interestingly, the aging phenotypes of mice suffering from hypovitaminosis D (VDR<sup>-/-</sup>) and CYP27B1<sup>-/-</sup> mice) are quite similar to those suffering from hypervitaminosis D (including FGF-23<sup>-/-</sup> and Klotho<sup>-/-</sup> mice). Consequently, it has been hypothesized that thus, both hypo- and hypervitaminosis D may enhance aging. Aging seems to show a U-shaped response curve to vitamin D status, and, therefore normovitaminosis D seems to be important for preventing premature aging. Additionally, laboratory investigations have now convincingly shown that vitamin D compounds protect the skin against the hazardous effects of various skin aging-inducing agents, including ultraviolet (UV) radiation. In conclusion, these findings support the concept that UV-radiation exerts both skin aging -promoting and -inhibiting effects, the latter via induction of cutaneous vitamin D synthesis. Future studies will clarify the effect of vitamin D compounds on expression and function of potential key regulators of skin aging, such as TAp63 or the IGF-1 signaling pathway. Furthermore, the efficacy of topically applied vitamin D compounds in the prevention of skin aging has to be evaluated in future clinical trials.

#### Source

Reichrath J. Unraveling hidden secrets: The role of vitamin D in skin aging. *Dermato-Endocrinology* 43:241-44, 2012.

#### **Botanicals in Dermatology: An Evidence based Review**

#### ABSTRACT

Botanical extracts and single compounds are increasingly used in cosmetics but also in over-the-counter drugs and food supplements. The focus of the present review is on controlled clinical trials with botanicals in the treatment of acne, inflammatory skin diseases, skin infections, UV-induced skin damage, skin cancer, alopecia, vitiligo, and wounds. Studies with botanical cosmetics and drugs are

discussed, as well as studies with botanical food supplements. Experimental research on botanicals was considered to a limited extent when it seemed promising for clinical use in the near future. In acne therapy, Mahonia, tea tree oil, and *Saccharomyces* may have the potential to become standard treatments. Mahonia, Hypericum, Glycyrrhiza and some traditional Chinese medicines appear promising for atopic dermatitis. Some plant-derived substances like dithranol and methoxsalen (8-methoxypsoralen) [in combination with UVA] are already accepted as standard treatments in psoriasis; Mahonia and Capsicum (capsaicin) are the next candidates suggested by present evidence. Oral administration and topical application of antioxidant plant extracts (green and black tea, carotenoids, coffee, and many flavonoids from fruits and vegetables) can protect skin from UV-induced erythema, early aging, and irradiation-induced cancer. Hair loss and vitiligo are also traditional fields of application for botanicals. According to the number and quality of clinical trials with botanicals, the best evidence exists for the treatment of inflammatory skin diseases, i.e. atopic dermatitis and psoriasis. However, many more controlled clinical studies are needed to determine the efficacy and risks of plant-derived products in dermatology. Safety aspects, especially related to sensitization and photodermatitis, have to be taken into account. Therefore, clinicians should not only be informed of the beneficial effects but also the specific adverse effects of botanicals used for dermatologic disorders and cosmetic purposes.

#### Source

Reuter J et al. Botanicals in Dermatology: An Evidence based Review. *Am J Clin Dermatol* 11:247-67, 2010.

**Oral green tea catechin metabolites are incorporated into human skin and protect against UV radiation-induced cutaneous inflammation in association with reduced production of pro-inflammatory eicosanoid 12-hydroxyeicosatetraenoic acid**

#### ABSTRACT

Green tea catechins (GTC) reduce UV radiation (UVR)-induced inflammation in experimental models, but human studies are scarce and their cutaneous bioavailability and mechanism of photoprotection are unknown. We aimed to examine oral GTC cutaneous uptake, ability to protect human skin against erythema induced by a UVR dose range and impact on potent cyclooxygenase- and lipoxygenase-produced mediators of UVR inflammation, PGE2 and 12-hydroxyeicosatetraenoic acid (12-HETE), respectively. In an open oral intervention study, sixteen healthy human subjects (phototype I/II) were given low-dose GTC (540 mg) with vitamin C (50 mg) daily for 12 weeks. Pre- and post-supplementation, the buttock skin was exposed to UVR and the resultant erythema quantified. Skin blister fluid and biopsies were taken from the unexposed and the UVR-exposed skin 24 h after a pro-inflammatory UVR challenge (three minimal erythema doses). Urine, skin tissue and fluid were analysed for catechin content and skin fluid for PGE2 and 12-HETE by liquid chromatography coupled to tandem MS. A total of fourteen completing subjects were supplement compliant (twelve female, median 42.5 years, range 29-59 years). Benzoic acid levels were increased in skin fluid post-supplementation (P= 0.03), and methylated gallic acid and several intact catechins and hydroxyphenyl-valerolactones were detected in the skin tissue and fluid. AUC analysis for UVR erythema revealed reduced response post-GTC (P= 0.037). Pre-supplementation, PGE2 and 12-HETE were UVR induced (P= 0.003, 0.0001). After GTC, UVR-induced 12-HETE reduced from mean 64 (sd 42) to 41 (sd 32) pg/μl (P= 0.01), while PGE2 was unaltered. Thus, GTC intake results in the incorporation of catechin metabolites into human skin associated with abrogated UVR-induced 12-HETE; this may contribute to protection against sunburn inflammation and potentially longer-term UVR-mediated damage.

#### Source

Rhodes LE et al. Oral green tea catechin metabolites are incorporated into human skin and protect against UV radiation-induced cutaneous inflammation in association with reduced production of pro-inflammatory eicosanoid 12-hydroxyeicosatetraenoic acid. Br

#### Discovering the link between nutrition and skin aging

#### ABSTRACT

Skin has been reported to reflect the general inner-health status and aging. Nutrition and its reflection on skin has always been an interesting topic for scientists and physicians throughout the centuries worldwide. Vitamins, carotenoids, tocopherols, flavonoids and a variety of plant extracts have been reported to possess potent anti-oxidant properties and have been widely used in the skin care industry either as topically applied agents or oral supplements in an attempt to prolong youthful skin appearance. This review will provide an overview of the current literature "linking" nutrition with skin aging.

#### Source

Schagen S et al. Discovering the link between nutrition and skin aging. Review. Dermato-Endocrinol 4:298-307, 2012.

#### Carotenoids and carotenoids plus vitamin E protect against ultraviolet light-induced erythema in humans

#### ABSTRACT

##### BACKGROUND:

Carotenoids and tocopherols, known to be efficient antioxidants and capable of scavenging reactive oxygen species generated during photooxidative stress, may protect the skin from ultraviolet light-induced erythema. b-Carotene is widely used as an oral sun protectant but studies on its protective effects are scarce.

##### OBJECTIVE:

The objective of this study was to investigate the protective effects of oral

supplementation with carotenoids and a combination of carotenoids and vitamin E against the development of erythema in humans.

##### DESIGN:

A carotenoid supplement (25 mg total carotenoids/d) and a combination of the carotenoid supplement and vitamin E [335 mg (500 IU) RRR-a-tocopherol/d] were given for 12 wk to healthy volunteers. Erythema was induced by illumination with a blue-light solar simulator. Serum b-carotene and a-tocopherol concentrations and skin carotenoid levels were assessed by HPLC and reflection photometry.

##### RESULTS:

Serum b-carotene and a-tocopherol concentrations increased with supplementation. Erythema on dorsal skin (back) was significantly diminished ( $P < 0.01$ ) after week 8, and erythema suppression was greater with the combination of carotenoids and vitamin E than with carotenoids alone.

##### CONCLUSION:

The antioxidants used in this study provided protection against erythema in humans and may be useful for diminishing sensitivity to ultraviolet light.

#### Source

Stahl, W et al. Carotenoids and carotenoids plus vitamin E protect against ultraviolet light-induced erythema in humans. Am J Clin Nutr 71:795-8, 2000.

#### Vitamin D controls T cell antigen receptor signaling and activation of human T cells

#### ABSTRACT

Phospholipase C (PLC) isozymes are key signaling proteins downstream of many extracellular stimuli. Here we show that naive human T cells had very low expression of PLC-gamma1 and that this correlated with low T cell antigen receptor (TCR) responsiveness in naive T cells. However, TCR triggering led to an upregulation of approximately 75-fold in PLC-gamma1 expression, which correlated

with greater TCR responsiveness. Induction of PLC-gamma1 was dependent on vitamin D and expression of the vitamin D receptor (VDR). Naive T cells did not express VDR, but VDR expression was induced by TCR signaling via the alternative mitogen-activated protein kinase p38 pathway. Thus, initial TCR signaling via p38 leads to successive induction of VDR and PLC-gamma1, which are required for subsequent classical TCR signaling and T cell activation.

#### Source

von Essen MR, et al. Vitamin D controls T cell antigen receptor signaling and activation of human T cells. Nat Immunol. 2010 Apr;11(4):344-9.

## WEIGHT MANAGEMENT

#### Vitamin D status and its relation to muscle mass and muscle fat in young women

#### ABSTRACT

##### CONTEXT:

Vitamin D insufficiency has now reached epidemic proportions and has been linked to increased body fat and decreased muscle strength. Whether vitamin D insufficiency is also related to adipose tissue infiltration in muscle is not known.

##### OBJECTIVE:

The objective of the study was to examine the relationship between serum 25-hydroxyvitamin D (25OHD) and the degree of fat infiltration in muscle.

##### DESIGN:

This was a cross-sectional study.

##### OUTCOME MEASURES

##### AND SUBJECTS:

Measures were anthropometric measures, serum 25OHD radioimmunoassay values, and computed tomography (CT) values of fat, muscle mass, and percent muscle fat in 90 postpubertal females, aged 16-22 yr, residing in California.

##### RESULTS:

Approximately 59% of subjects were



25OHD insufficient ( $< \text{ or } = 29 \text{ ng/ml}$ ), of which 24% were deficient ( $< \text{ or } = 20 \text{ ng/ml}$ ), whereas 41% were sufficient ( $> \text{ or } = 30 \text{ ng/ml}$ ). A strong negative relationship was present between serum 25OHD and CT measures of percent muscle fat ( $r = -0.37$ ;  $P < 0.001$ ). In contrast, no relationship was observed between circulating 25OHD concentrations and CT measures of thigh muscle area ( $r = 0.16$ ;  $P = 0.14$ ). Multiple regression analysis indicated that the relation between 25OHD and muscle adiposity was independent of body mass or CT measures of sc and visceral fat. Percent muscle fat was significantly lower in women with normal serum 25OHD concentrations than in women with insufficient levels and deficient levels ( $3.15 \pm 1.4$  vs.  $3.90 \pm 1.9$ ;  $P = 0.038$ ).

#### CONCLUSIONS:

We found that vitamin D insufficiency is associated with increased fat infiltration in muscle in healthy young women.

#### Source

Gilsanz V, et al. Vitamin D status and its relation to muscle mass and muscle fat in young women. *J Clin Endocrinol Metab*. 2010 Apr;95(4):1595-601.

#### Serum 25-Hydroxyvitamin D is Independently Associated with High Density Lipoprotein Cholesterol and the Metabolic Syndrome in Men and Women

#### ABSTRACT

##### BACKGROUND:

Low vitamin D status has been associated with markers of cardiovascular disease risk.

##### OBJECTIVE:

This cross-sectional study assessed the relationships between serum 25-hydroxyvitamin D [25(OH)D] and selected markers for cardiovascular disease risk, including metabolic syndrome and its components, in adult men and women.

##### METHODS:

Fasting blood samples, anthropometric measurements, and blood pressure were assessed in 257 men and women. Dietary intake was assessed with food frequency and dietary supplement questionnaires.

##### RESULTS:

Total vitamin D intake and that from dietary

supplements were significantly associated with increasing serum 25(OH)D tertile (both  $P < .001$ ). Mean $\pm$ SEM serum high-density lipoprotein cholesterol (HDL-C) increased in a graded fashion ( $P < .001$ ) from the lowest ( $48.4 \pm 1.8 \text{ mg/dL}$ ) to the highest ( $62.3 \pm 2.1 \text{ mg/dL}$ ) 25(OH)D tertile. The relationship between 25(OH)D and HDL-C remained significant ( $P < .001$ ) after adjustment for established determinants of the HDL-C, with each 10-ng/mL increase in 25(OH)D associated with a 4.2-mg/dL increase in HDL-C concentration. Serum triglycerides ( $P = .008$ ), waist circumference ( $P < .001$ ), and body mass index ( $P < .001$ ) showed graded, inverse relationships with 25(OH)D tertile, and the prevalence of metabolic syndrome decreased significantly from the lowest to the highest 25(OH)D tertile (31%, 14%, and 10%, respectively,  $P$  for trend = .001).

#### CONCLUSIONS:

Lower serum 25(OH)D is associated with the metabolic syndrome and adverse values for some metabolic syndrome risk factors, particularly the HDL-C concentration. Research is warranted to assess whether increasing vitamin D intake will improve the metabolic cardiovascular risk factor profile.

#### Source

Maki KC, et al. Serum 25-Hydroxyvitamin D is Independently Associated with High Density Lipoprotein Cholesterol and the Metabolic Syndrome in Men and Women. *J Clin Lipidology*. 2009 Jul; 3(4):289-96

#### Whole- and refined-grain intakes are differentially associated with abdominal visceral and subcutaneous adiposity in healthy adults: the Framingham Heart Study

#### ABSTRACT

##### BACKGROUND:

Observational studies have linked higher intakes of whole grains to lower abdominal adiposity; however, the association between whole- and refined-grain intake and body fat compartments has yet to be reported.

##### OBJECTIVE:

Different aspects of diet may be differentially

related to body fat distribution. The purpose of this study was to assess associations between whole- and refined-grain intake and abdominal subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT).

#### DESIGN:

Cross-sectional associations between whole- and refined-grain intakes, waist circumference measures, and abdominal SAT and VAT volumes were examined in 2834 Framingham Heart Study participants (49.4% women; age range: 32-83 y). Dietary information was assessed with the use of a semiquantitative food-frequency questionnaire.

#### RESULTS:

Whole-grain intake was inversely associated with SAT (2895 compared with 2552  $\text{cm}^3$  in the lowest compared with the highest quintile category,  $P$  for trend  $< 0.001$ ) and VAT (1883 compared with 1563  $\text{cm}^3$ ,  $P$  for trend  $< 0.001$ ), after adjustment for age, sex, current smoking status, total energy, and alcohol intake. In contrast, refined-grain intake was positively associated with SAT (2748 compared with 2934  $\text{cm}^3$ ,  $P$  for trend = 0.01) and VAT (1727 compared with 1928  $\text{cm}^3$ ,  $P$  for trend  $< 0.001$ ) in multivariable models. When SAT and VAT were evaluated jointly, the  $P$  value for SAT was attenuated ( $P = 0.28$  for whole grains,  $P = 0.60$  for refined grains), whereas VAT remained associated with both whole grains ( $P < 0.001$ ) and refined grains ( $P < 0.001$ ).

#### CONCLUSIONS:

Increasing whole-grain intake is associated with lower VAT in adults, whereas higher intakes of refined grains are associated with higher VAT. Further research is required to elicit the potential mechanisms whereby whole- and refined-grain foods may influence body fat distribution.

#### Source

McKeown NM, et al. Whole- and refined-grain intakes are differentially associated with abdominal visceral and subcutaneous adiposity in healthy adults:

the Framingham Heart Study. Am J Clin Nutr. 2010 Nov;92(5):1165-71. Epub 2010 Sep 29.

### Calcium and vitamin D supplementation is associated with decreased abdominal visceral adipose tissue in overweight and obese adults

#### ABSTRACT

##### BACKGROUND:

Several studies suggest that calcium and vitamin D (CaD) may play a role in the regulation of abdominal fat mass.

##### OBJECTIVE:

This study investigated the effect of CaD-supplemented orange juice (OJ) on weight loss and reduction of visceral adipose tissue (VAT) in overweight and obese adults (mean  $\pm$  SD age: 40.0  $\pm$  12.9 y).

##### DESIGN:

Two parallel, double-blind, placebo-controlled trials were conducted with either regular or reduced-energy (lite) orange juice. For each 16-wk trial, 171 participants were randomly assigned to 1 of 2 groups. The treatment groups consumed three 240-mL glasses of OJ (regular or lite) fortified with 350 mg Ca and 100 IU vitamin D per serving, and the control groups consumed either unfortified regular or lite OJ. Computed tomography scans of VAT and subcutaneous adipose tissue were performed by imaging a single cut at the lumbar 4 level.

##### RESULTS:

After 16 wk, the average weight loss ( 2.45 kg) did not differ significantly between groups. In the regular OJ trial, the reduction of VAT was significantly greater ( $P = 0.024$ ) in the CaD group ( $-12.7 \pm 25.0$  cm<sup>2</sup>) than in the control group ( $-1.3 \pm 13.6$  cm<sup>2</sup>). In the lite OJ trial, the reduction of VAT was significantly greater ( $P = 0.039$ ) in the CaD group ( $-13.1 \pm 18.4$  cm<sup>2</sup>) than in the control group ( $-6.4 \pm 17.5$  cm<sup>2</sup>) after control for baseline VAT. The effect of calcium and vitamin D on VAT remained highly significant when the results of the 2 trials were combined ( $P = 0.007$ ).

##### CONCLUSIONS:

The findings suggest that calcium and/or vitamin D supplementation contributes to a beneficial reduction of VAT. This

trial is registered at clinicaltrials.gov as NCT00386672, NCT01363115.

#### Source

Rosenblum JL et al. Calcium and vitamin D supplementation is associated with decreased abdominal visceral adipose tissue in overweight and obese adults. Am J Clin Nutr 95:101-8, 2011.

### Greater Whole-Grain Intake Is Associated with Lower Risk of Type 2 Diabetes, Cardiovascular Disease, and Weight Gain

#### ABSTRACT

Whole-grain and high fiber intakes are routinely recommended for prevention of vascular diseases; however, there are no comprehensive and quantitative assessments of available data in humans. The aim of this study was to systematically examine longitudinal studies investigating whole-grain and fiber intake in relation to risk of type 2 diabetes (T2D), cardiovascular disease (CVD), weight gain, and metabolic risk factors. We identified 45 prospective cohort studies and 21 randomized-controlled trials (RCT) between 1966 and February 2012 by searching the Cumulative Index to Nursing and Allied Health Literature, Cochrane, Elsevier Medical Database, and PubMed. Study characteristics, whole-grain and dietary fiber intakes, and risk estimates were extracted using a standardized protocol. Using random effects models, we found that compared with never/rare consumers of whole grains, those consuming 48-80 g whole grain/d (3-5 serving/d) had an ~26% lower risk of T2D [RR = 0.74 (95% CI: 0.69, 0.80)], ~21% lower risk of CVD [RR = 0.79 (95% CI: 0.74, 0.85)], and consistently less weight gain during 8-13 y (1.27 vs 1.64 kg;  $P = 0.001$ ). Among RCT, weighted mean differences in post-intervention circulating concentrations of fasting glucose and total and LDL-cholesterol comparing whole-grain intervention groups with controls indicated significantly lower concentrations after whole-grain interventions [differences in fasting glucose: -0.93 mmol/L (95% CI: -1.65, -0.21), total cholesterol: -0.83 mmol/L

(-1.23, -0.42); and LDL-cholesterol: -0.82 mmol/L (-1.31, -0.33)]. [corrected] Findings from this meta-analysis provide evidence to support beneficial effects of whole-grain intake on vascular disease prevention. Potential mechanisms responsible for whole grains' effects on metabolic intermediates require further investigation in large intervention trials.

#### Source

Ye EQ et al. Greater Whole-Grain Intake Is Associated with Lower Risk of Type 2 Diabetes, Cardiovascular Disease, and Weight Gain. J Nutr 142:1304-13, July, 2012 Epub May 30, 2012].