

In Brief

With the exceptions of folate for prevention of birth defects and calcium for prevention of bone disease, currently there is no evidence of benefit from vitamin or mineral supplementation in diabetic patients without underlying deficiencies. Given the recent revelations about antioxidant vitamins, it is prudent to refrain from using vitamin E, vitamin C, or vitamin A in excess of the Dietary Reference Intakes.

The Role of Micronutrients in Managing Diabetes

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Although medical nutrition therapy is a cornerstone of the management of diabetes, several areas of uncertainty in the dietary guidelines still exist.¹ The degree of uncertainty is especially high in the area of assessing micronutrient status and the role of micronutrients in the pathogenesis of diabetes and its complications.^{2,3} Laboratory methods available for measuring the status of most micronutrients are still unsatisfactory.

In the early 1990s, the Food and Nutrition Board revised the Recommended Dietary Allowance (RDA) system, and a new set of nutrient reference values was born: Dietary Reference Intakes (DRIs). There are four types of DRIs: Estimated Average Requirement (EAR), RDA, Adequate Intake (AI), and Tolerable Upper Intake Level (UL).

There has been considerable subjectivity in assigning DRI values for many micronutrients. In addition, the lack of evidence showing that antioxidant vitamins result in any beneficial health outcomes despite the overwhelming evidence of increased oxidative load in diabetes has left health care providers with a significant degree of confusion about whether micronutrient supplementation should be recommended for people with diabetes.^{4,5}

This article reviews the status of evidence for select minerals and vitamins in diabetes care and the advantages or disadvantages of supplementation of the diet with micronutrients and herbal extracts.

MINERALS

People with uncontrolled hyperglycemia, especially those on chronic diuretic therapy, are prone to develop deficiencies in some minerals, notably potassium, magnesium, and zinc.^{2,3} Deficiencies of certain minerals such as potassium, magnesium, and possibly zinc and chromium may predispose one to carbohydrate intolerance.

The need for potassium or magnesium replacement is easily accepted because the effects of overt potassium or magnesium deficiency, especially on the cardiovascular system and skeletal muscles, are profound and readily detectable. The deficiency state of potassium and magnesium is relatively easy to detect based on low serum levels. The consequences of zinc and chromium deficiency are slow to emerge, and the need for supplementation is more difficult to ascertain.¹⁻³

Chromium

Several small studies have found that chromium supplementation improves glucose intolerance, gestational diabetes, and corticosteroid-induced diabetes.⁶⁻⁸ Two randomized, placebo-controlled studies in Chinese subjects with diabetes have shown that chromium supplementation has beneficial effects on glycemic control.^{9,10} Unfortunately, chromium status was not evaluated in these studies at baseline or after supplementation.

Other well-designed studies have failed to demonstrate any significant benefit of chromium supplementation in people with diabetes⁶ and have not

shown any benefit in reducing body weight.¹¹ The earlier studies used chromium chloride preparation. More recent studies have used chromium picolinate, which has better bioavailability. The dose and formulations of chromium used are important variables in the outcomes of the clinical trials.

Given the current body of evidence, chromium supplementation in any formulation available cannot be recommended as a tool for weight loss or diabetes management.¹²

Zinc

People with uncontrolled diabetes have increased zinc losses in the urine. Ordinarily, these losses are counterbalanced by enhanced zinc absorption in the gut.^{2,3} However, it is conceivable that the latter compensatory mechanism may not be sufficient to prevent zinc deficiency in some people.

Small studies in older subjects with diabetes have suggested some benefit in healing skin ulcerations with zinc supplementation.^{2,3,13} Reliable laboratory techniques to measure zinc status are not clinically available, and clinical trials with zinc supplementation in diabetic subjects are very small and have yielded inconsistent results. A recent observational study reported a significant inverse association of dietary intakes and serum levels of zinc and selenium with gestational diabetes.¹⁴ These observations merit additional confirmatory studies.

If one suspects zinc deficiency, especially in high-risk patients such as those with prolonged glycosuria and diuretic therapy, one can consider supplementation of zinc sulfate, 220 mg three times daily. This should be initiated for no more than 3 months because prolonged zinc supplementation may inhibit copper absorption and adversely affect lipid profiles.^{2,3,13}

Calcium

Recent studies have shown that calcium and vitamin D are not only required for skeletal health but also may have a role in immune modulation and pancreatic insulin secretion and action.^{15,16} The recommended daily intake varies according to age of the subject and, in females, the menopausal state. At the present time, there is no reason to recommend higher calcium and vitamin D intake for people with diabetes compared to an age-matched cohort of nondiabetic people. The Institute of Medicine recommen-

dations for adequate daily intake of vitamin D are 200 IU for children and adults ≤ 50 years of age, 400 IU for adults 51–70 years of age, and 600 IU for adults ≥ 71 years of age. People living in northern latitudes often require higher amounts (at least 800 IU).¹⁵

Cholecalciferol (vitamin D₃) is preferred for replacement because it has a longer half-life,¹⁷ and its measurement in serum levels is less likely to be fraught with uncertainties. However, high-dose formulations of cholecalciferol are not readily available, and therefore plant-derived ergocalciferol (vitamin D₂) is more commonly prescribed.

Serum 25-hydroxy vitamin D levels should be measured after 3 months of supplementation. If serum levels of 25-hydroxy vitamin D are not normalized at that time, then work up for malabsorption, particularly gluten enteropathy, should be considered.

Vanadium

Vanadium has a significant effect on glucose metabolism. However, clinical studies have failed to show evidence of efficacy of vanadium salts in diabetes and have found that there is potential for toxicity.¹⁸ New organo-vanadium compounds with higher potency and less toxicity are under investigation as a potential treatment of diabetes.¹⁸

Selenium

Selenium is an important component of selenoproteins, which are implicated in modulating oxidative stress and regulating thyroid hormone activity.¹⁹ In five trials (four with high risk of bias), selenium seemed to show significant beneficial effect on gastrointestinal cancer occurrence.²⁰

There are also some supportive data to suggest that selenium may prevent prostate cancer. However, a recent randomized, placebo-controlled trial in 35,533 men given 200 μ g per day of L-selenomethionine or matched placebo did not show any favorable effect on the incidence of prostate cancer.²¹ In the same trial, 400 IU per day of vitamin E either alone or in combination with selenium also did not prevent prostate cancer.²¹ The potential cancer-preventive effect of selenium should be tested in adequately conducted randomized trials.

Selenium deficiency may occur in geographical areas where the agricultural soil is depleted of selenium. In these populations, selenium prevention should be pursued. However, excess

selenium may cause selenosis, affecting the liver, skin, nails, and hair.¹⁹ In addition, two recent studies examining the relationship between serum selenium levels and the prevalence of diabetes among U.S. adults found that high serum selenium levels were positively associated with the prevalence of diabetes,²² that selenium supplementation did not prevent type 2 diabetes, and that it may increase the risk for the disease.²³ Thus, the indiscriminant use of selenium supplements should be discouraged until more randomized, controlled trials examine their effects on human health.

VITAMINS

Vitamin A, Carotenoids, and Retinoids

Vitamin A is essential for normal vision and for an effective functioning of the immune system.^{2,3} Because of its role in cell differentiation, it may have a role in the emergence and propagation of neoplastic disease. A number of carotenoids, especially beta-carotenoids, are considered to be pro-vitamins because of their ability to convert to vitamin A in the liver. Retinoids derive from natural vitamin A products and have some properties similar to carotenoids.

There is no evidence that people with diabetes are at risk of vitamin A deficiency, and therefore there is no reason to recommend vitamin A in amounts beyond the DRIs.^{2,3} Indeed, excess vitamin A consumption may have deleterious effects on health. These adverse effects include increased risk of liver fibrosis, increased incidence of lung cancer (especially in smokers and in those exposed to asbestos), increased risk of osteoporosis, and increased incidence of birth defects when vitamin A in excess of 10,000 IU per day is taken before the seventh week of gestation.^{24–29} A recent meta-analysis of the experimental data suggested that beta-carotene in combination with vitamin A and vitamin E significantly increased mortality.²⁰ Increased yellowing of the skin and belching were nonserious adverse effects of excess beta-carotene.²⁰

Select B Vitamins

Folate and folic acid are forms of a water-soluble B vitamin designated as vitamin B₉. Folate occurs naturally in food, and folic acid is the synthetic form of this vitamin.

Deficiency results in a macrocytic anemia and elevated levels of homocysteine. Plasma homocysteine concentration in type 2 diabetes correlates with age, creatinine, folate, and vitamin B12 but not with diabetes-related variables such as duration, current degree of control, or presence of complications.³⁰ Folic acid might also have favorable effects on cognition in older adults.¹³ The realization that folate has a pivotal role in preventing birth defects has prompted folate fortification of wheat and grain products in the United States.¹

Because of the association between elevated serum homocysteine levels and cardiovascular disease (CVD), there has been increasing interest in folate supplementation to lower homocysteine. However, interventional trials with folate and vitamin B6 and B12 supplementation have failed to prevent cardiovascular events despite lowering homocysteine levels.^{31,32} In a study of 5,442 women who were U.S. health professionals > 42 years of age with either a history of CVD or three or more coronary risk factors, daily intake of a combination pill of 2.5 mg of folic acid, 50 mg of vitamin B6, and 1 mg of vitamin B12 did not reduce total cardiovascular events after 7.3 years of treatment and follow-up despite significant homocysteine lowering.³¹ Similarly, combined folic acid, vitamin B6, and vitamin B12 treatment had no significant effect on overall risk of total invasive cancer or breast cancer among women.³³

The combination of folic acid, pyridoxine hydrochloride, and cyanocobalamin may have protective effects against age-related macular degeneration (AMD). In the Women's Antioxidant and Folic Acid Cardiovascular Study, participants were randomly assigned to receive a combination of folic acid (2.5 mg/day), pyridoxine hydrochloride (50 mg/day), and cyanocobalamin (1 mg/day) or placebo. A total of 5,205 of these women did not have a diagnosis of AMD at baseline and were included in this analysis. The results indicated that daily supplementation with folic acid, pyridoxine, and cyanocobalamin may reduce the risk of AMD.³⁴

There are no health concerns with folate supplementation except for aggravating vitamin B12 deficiency and occasionally causing seizures in people with epilepsy and marginal folate status who are receiving anti-

convulsants that are known to increase folate catabolism.^{2,3}

The role of vitamins B1, B6, and B12 in the treatment of diabetic neuropathy has not been established and cannot be recommended as a standard or routine therapeutic option.¹⁻³

Vitamin B3 is made up of niacin (nicotinic acid) and its amide. In a study of newly diagnosed subjects with type 1 diabetes,³⁵ nicotinamide was found to preserve β -cell mass. However, the number of subjects enrolled in this study was small, and the clinical utility of nicotinamide in this population is not established.

Vitamin C (Ascorbic Acid)

Ascorbic acid has potent antioxidant activity. However, under certain experimental conditions, it can also be a pro-oxidant.⁴ Although the evidence is not conclusive, people with diabetes may have depleted tissue stores of vitamin C. The tissue uptake of dehydroascorbate can be prevented by high ambient blood glucose levels.³⁶

The rationale for use of vitamin C in the diabetic population is based on its potential effects on reducing atherosclerotic plaque formation, preventing microangiopathy, improving vascular integrity, and aiding in wound healing.^{2,3,13} However, supplementation with vitamin C in interventional trials has not reduced the risk of cancer or cardiovascular disease.³⁷⁻⁴⁰ In the Women's Antioxidant Cardiovascular Study, supplementation with vitamin C (500 mg of ascorbic acid daily), vitamin E (600 IU of alpha-tocopherol every other day), or beta-carotene (50 mg every other day) offered no benefits in the primary prevention of total cancer incidence or cancer mortality.³⁷

Consumption of vitamin C in amounts > 1 g/day can cause some abdominal bloating and osmotic diarrhea.¹³ There is no reason to recommend vitamin C intake in excess of the DRIs. Smokers must consume larger amounts of ascorbic acid to reach comparable plasma levels of nonsmokers, most likely because of an increased turnover.³ People with diabetes can achieve adequate intake of vitamin C through consumption of five daily servings of fruits and vegetables. In individuals who are incapable of getting sufficient amounts from dietary sources, supplementation of ascorbic acid is reasonable.^{2,3,13}

Vitamin E (Tocopherols)

Vitamin E is also a potent antioxidant. In experimental studies, vitamin E supplementation in excess of DRIs was capable of reducing LDL oxidation and stabilized platelet membranes.³ Observational studies have suggested that vitamin E supplements may confer cardioprotective effects.⁵ However, interventional trials including those that have enrolled a large number of people with diabetes⁴¹ have not supported the use of vitamin E to reduce cardiovascular risk.⁵ A recent meta-analysis of the experimental data has suggested that vitamin E supplements may actually increase mortality.⁴⁰

People with diabetes generally do not have vitamin E deficiency. Indeed, the plasma and platelet content of vitamin E may be increased in diabetes.^{2,3} Although consumption in the range of 1,000 IU of vitamin E is considered relatively safe, there has been some concern associated with this practice.⁴⁰ Progression of retinitis pigmentosa and increased incidence of hemorrhagic strokes have been linked to excessive consumption of vitamin E.⁴⁰ Consumption in excess of DRIs is not recommended. If an individual chooses to use supplements, the dose should be limited to \leq 400 IU/day.

OTHER MICRONUTRIENTS

Herbal Preparations

Some herbal preparations have been shown to have modest short-term beneficial effects on glycemia.⁴² Well-designed, randomized, controlled trials in small numbers of subjects have shown some benefits of *Coccinia indica* and American ginseng.⁴² Other supplements that may have favorable effects on glycemic control include *Gymnema sylvestre*, *Aloe vera*, *Momordica charantia*, and *Nopal*.⁴²

Some may have favorable effects on body weight. However, in a review of the available literature, the evidence for any role of herbal products in reducing body weight was not convincing, and the authors concluded that none of the supplements reviewed can be recommended for over-the-counter use.⁴³

Commercially available products vary in their active ingredients. In addition, some preparations have been found to surreptitiously include pharmaceutical agents that cause hypoglycemia. Herbal preparations also have the potential to interact with other medications. Therefore, it

is important for health care providers to be aware when their patients with diabetes are using these products.

Alpha-Lipoic Acid

Alpha-lipoic acid (LA) is a naturally occurring dithiol micronutrient with potent antioxidant properties.⁴⁴ LA scavenges free radicals, chelates transition metal ions, and increases cytosolic glutathione and vitamin C levels. It has an essential role as a cofactor for mitochondrial bioenergetic enzymes.

The potential beneficial effects of LA on both prevention and treatment of diabetes have been shown in multiple studies. LA has been proven to have a role in preventing β -cell destruction and enhancing insulin sensitivity. Unfortunately, the improvement in insulin sensitivity after oral administration of LA is < 20% of the improvement seen after intravenous administration.⁴⁴ This limits the clinical utility of this compound.

The antioxidant effects of LA may also be helpful in slowing the development of diabetic neuropathy.⁴⁴ Although the role of long-term supplementation is less clear, there is evidence to suggest that oral LA at a dose of 600–1,800 mg/daily may be beneficial in the treatment of diabetic peripheral neuropathy and cardiovascular autonomic neuropathy.⁴⁴

MICRONUTRIENTS AS ANTIOXIDANTS

Several micronutrients have potent antioxidant properties. These include carotenoids, vitamins E and C, selenium, and some of the B vitamins, notably folate, pyridoxine, and cyanocobalamin.

Diabetes, especially when poorly controlled, is associated with increased accumulation of oxidative end products.^{45,46} The increased oxidative stress in diabetes is the result of excess glycemia and depletion of the antioxidant defense system.⁴ Because increased oxidative stress has been implicated in the increased risk of cardiovascular disease and cancer, the association between consumption of antioxidant vitamins and minerals and reduced CVD risk is understandable. However, measurements of individual antioxidant vitamins have not consistently been shown to be deficient in people with diabetes. In the recently published Physicians' Health Study II, 400 IU of vitamin E every other day and 500 mg of vitamin C daily did not have any

benefit on decreasing the incidence of major cardiovascular events.⁴⁷ In contrast, vitamin E was associated with an increased risk of hemorrhagic stroke.⁴⁷ In addition, neither vitamin E nor vitamin C supplementation reduced the risk of prostate or total cancer.⁴⁰ In the Women's Health Study,⁴⁸ vitamin E supplements (600 mg every other day) did not protect healthy women against heart attacks, strokes, or cancer. A meta-analysis of 68 randomized trials with 232,606 participants concluded that treatment with vitamin A, vitamin E, and beta-carotene may well increase mortality.⁴⁰ On the other hand, the possible effects of vitamin C and selenium on mortality require additional study.⁴⁰

The discrepancy among the results of interventional trials with antioxidant vitamins and the known increased oxidative load and its consequences in diabetes are unexpected and cannot be readily explained at the present time.

CONCLUSIONS AND RECOMMENDATIONS

People with poorly controlled diabetes are susceptible to multiple micronutrient deficiencies.^{1–4} Some of these micronutrients have potent antioxidant activity. It is not known whether the ingestion of antioxidant vitamins could delay or perhaps reverse the oxidative damage.

People with diabetes should be educated about the importance of acquiring daily vitamin and mineral requirements from natural food sources. In select groups such as the elderly, pregnant or lactating women, strict vegetarians, or those on calorie-restricted diets, supplementation with a multivitamin preparation is advisable.¹ However, vitamin and mineral supplementation in pharmacological doses should be viewed as therapeutic intervention and, just as with medications, should be subjected to placebo-controlled trials to demonstrate safety and efficacy.

At the present time, there is no evidence of benefit from vitamin or mineral supplementation in people with diabetes who do not have underlying deficiencies. Exceptions include folate for prevention of birth defects and calcium for prevention of bone disease.¹ Given the recent revelations about antioxidant vitamins, it is advisable to refrain from using vitamin E, vitamin C, or vitamin A in excess

of the DRIs. Tables listing the DRIs have been published and are available online.⁴⁹

One of the major differences between the recent DRI reports and the previous RDAs is the creation of a UL. The UL is different from excessive intake and toxicities. Intake levels at the upper UL should be interpreted as a "warning flag" but not as toxic levels. ULs could not be established for vitamin K, thiamin, riboflavin, vitamin B12, pantothenic acid, biotin, or carotenoids. In the absence of ULs, extra caution may be warranted in consuming levels above RDA or AI recommendations.

References

- ¹Franz MJ, Bantle JP, Beebe CA, Brunzell JD, Chiasson JL, Garg A, Holzmeister LA, Hoogwerf B, Mayer-Davis E, Mooradian AD, Purnell JQ, Wheeler M: Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. *Diabetes Care* 25:148–198, 2002
- ²Mooradian AD, Failla M, Hoogwerf B, Maryniuk M, Wylie-Rosett J: Selected vitamins and minerals in diabetes. *Diabetes Care* 17:464–479, 1994
- ³Mooradian AD: Micronutrients in diabetes mellitus. In *Drugs, Diet, and Disease*. Vol. 2. Ioannides C, Flatt PR, Eds. Hemel Hempstead, U.K., Ellis Horwood, 1999, p. 183–200.
- ⁴Mooradian AD: Antioxidants and diabetes. *Nestle Nutr Workshop Ser Clin Perform Programme* 11:107–122, 2006
- ⁵Hasanain B, Mooradian AD: Antioxidant vitamins and their influence in diabetes mellitus. *Curr Diabetes Rep* 2:448–456, 2002
- ⁶Cefalu WT, Hu FB: Role of chromium in human health and in diabetes. *Diabetes Care* 27:2741–2751, 2004
- ⁷Ryan GJ, Wanko NS, Redman AR, Cook CB: Chromium as adjunctive treatment for type 2 diabetes. *Ann Pharmacother* 37:876–885, 2003
- ⁸Althuis MD, Jordan NE, Ludington EA, Wittes JT: Glucose and insulin responses to dietary chromium supplements: a meta-analysis. *Am J Clin Nutr* 76:148–155, 2002
- ⁹Cheng N, Zhu X, Shi H, Wu W, Chi J, Cheng J, Anderson RA: Follow-up survey of people in China with type 2 diabetes mellitus consuming supplemental chromium. *J Trace Elements Exp Res* 12:55–60, 1999
- ¹⁰Anderson RA, Cheng N, Bryden NA, Polansky MM, Cheng N, Chi J, Feng J: Elevated intakes of supplemental chromium improve glucose and insulin variables in individuals with type 2 diabetes. *Diabetes* 46:1786–1791, 1997
- ¹¹Lukaski HC, Siders WA, Penland JG: Chromium picolinate supplementation in women: effects on body weight, composition, and iron status. *Nutrition*. 23:187–195, 2009

- ¹²Pittler MH, Stevinson C, Ernst E: Chromium picolinate for reducing body weight: meta-analysis of randomized trials. *Int J Obes Relat Metab Disord* 27:522–529, 2003
- ¹³Thurman J, Mooradian AD: Vitamin supplementation therapy in the elderly. *Drugs Aging* 11:433–449, 1997
- ¹⁴Bo S, Lezo A, Menato G, Gallo ML, Bardelli C, Signorile A, Berutti C, Massobrio M, Pagano GF: Gestational hyperglycemia, zinc, selenium, and antioxidant vitamins. *Nutrition* 21:186–191, 2005
- ¹⁵Holick MF: Vitamin D deficiency. *N Engl J Med* 357:266–281, 2007
- ¹⁶Rosen CJ: Postmenopausal osteoporosis. *N Engl J Med* 353:595–603, 2005
- ¹⁷Armas LA, Hollis BW, Heany RP: Vitamin D2 is much less effective than vitamin D3 in humans. *J Clin Endocrinol Metab* 89:5387–5391, 2004
- ¹⁸Srivastava AK, Mehdi MZ: Insulinomimetic and anti-diabetic effects of vanadium compounds. *Diabet Med* 22:2–13, 2005
- ¹⁹Boosalis MG: The role of selenium in chronic disease. *Nutr Clin Pract* 23:152–160, 2008
- ²⁰Bjelakovic G, Nikolova D, Simonetti RG, Gluud C: Antioxidant supplements for preventing gastrointestinal cancers. *Cochrane Database Syst Rev* 2008:CD004183
- ²¹Lippman SM, Klein EA, Goodman PJ, Lucia MS, Thompson IM, Ford LG, Parnes HL, Minasian LM, Gaziano JM, Hartline JA, Parsons JK, Bearden JD 3rd, Crawford ED, Goodman GE, Claudio J, Winquist E, Cook ED, Karp DD, Walther P, Lieber MM, Kristal AR, Darke AK, Arnold KB, Ganz PA, Santella RM, Albanes D, Taylor PR, Probstfield JL, Jagpal TJ, Crowley JJ, Meyskens FL Jr, Baker LH, Coltman CA Jr. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial. *JAMA* 301:39–51, 2009
- ²²Blevis J, Navas-Acien A, Guallar E: Serum selenium and diabetes in U.S. adults. *Diabetes Care* 30:829–834, 2007
- ²³Stranges S, Marshall JR, Natarajan R, Donahue RP, Trevisan M, Combs GF, Cappuccio FP, Ceriello A, Reid ME: Effects of long-term selenium supplementation on the incidence of type 2 diabetes: a randomized trial. *Ann Intern Med* 147:217–223, 2007
- ²⁴Lee IM, Cook NR, Manson JE, Buring JE, Hennekens CH: Beta-carotene supplementation and incidence of cancer and cardiovascular disease: the Women's Health Study. *J Natl Cancer Inst* 91:2102–2106, 1999
- ²⁵Hennekens CH, Buring JE, Manson JE, Stampfer M, Rosner B, Cook NR, Belanger C, LaMotte F, Gaziano JM, Ridker PM, Willett W, Peto R: Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. *N Engl J Med* 334:1145–1149, 1996
- ²⁶Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A, Keogh JP, Meyskens FL Jr, Valanis B, Williams JH Jr, Barnhart S, Cherniack MG, Brodtkin CA, Hammar S. Risk factors for lung cancer and for intervention effects in CARET: the Beta Carotene and Retinol Efficacy Trial. *J Natl Cancer Inst* 88:1550–1559, 1996
- ²⁷ATBC Cancer Prevention Study Group: The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med* 330:1029–1035, 1994
- ²⁸Melhus H, Michaelsson K, Kindmard A, Bergström R, Holmberg L, Mallmin H, Wolk A, Ljunghall S. Excessive dietary intake of vitamin A is associated with reduced bone mineral density and increased risk for hip fracture. *Ann Intern Med* 129:770–778, 1998
- ²⁹Rothman KJ, Moore LL, Singer MR, Nguyen U-SDT, Mannino S, Milunsky A: Teratogenicity of high vitamin A intake. *N Engl J Med* 333:1369–1373, 1995
- ³⁰Russo GT, Di Benedetto A, Giorda C, Alessi E, Crisafulli G, Ientile R, Di Cesare E, Jacques PF, Raimondo G, Cucinotta D: Correlates of total homocysteine plasma concentration in type 2 diabetes. *Eur J Clin Invest* 34:197–204, 2004
- ³¹Albert CM, Cook NR, Gaziano JM, Zaharris E, MacFadyen J, Danielson E, Buring JE, Manson JE: Effect of folic acid and B vitamins on risk of cardiovascular events and total mortality among women at high risk for cardiovascular disease: a randomized trial. *JAMA* 299:2027–2036, 2008
- ³²Bønaa KH, Njølstad I, Ueland PM, Schirmer H, Tverdal A, Steigen T, Wang H, Nordrehaug JE, Arnesen E, Rasmussen K; NORVIT Trial Investigators: Homocysteine lowering and cardiovascular events after acute myocardial infarction. *N Engl J Med* 354:1578–1588, 2006
- ³³Zhang SM, Cook NR, Albert CM, Gaziano JM, Buring JE, Manson JE: Effect of combined folic acid, vitamin B6, and vitamin B12 on cancer risk in women: a randomized trial. *JAMA* 300:2012–2021, 2008
- ³⁴Christen WG, Glynn RJ, Chew EY, Albert CM, Manson JE: Folic acid, pyridoxine, and cyanocobalamin combination treatment and age-related macular degeneration in women: the Women's Antioxidant and Folic Acid Cardiovascular Study. *Arch Intern Med* 169:335–341, 2009
- ³⁵Visalli N, Cavallo MG, Signore A, Baroni MG, Buzzetti R, Fioriti E, Mesturino C, Fiori R, Lucentini L, Matteoli MC, Crinò A, Corbi S, Spera S, Teodonio C, Paci F, Amoretti R, Pisano L, Suraci G, Multari G, Sulli N, Cervoni M, De Mattia G, Faldetta MR, Boscherini B, Pozzilli P. A multi-centre randomized trial of two different doses of nicotinamide in patients with recent-onset type 1 diabetes (the IMDIAB VI). *Diabetes Metab Res Rev* 15:181–185, 1999
- ³⁶Mooradian AD: Effect of ascorbate and dehydroascorbate on tissue uptake of glucose. *Diabetes* 36:1001–1004, 1987
- ³⁷Lin J, Cook NR, Albert C, Zaharris E, Gaziano JM, Van Denburgh M, Buring JE, Manson JE: Vitamins C and E and beta carotene supplementation and cancer risk: a randomized controlled trial. *J Natl Cancer Inst* 101:14–23, 2009
- ³⁸Cook NR, Albert CM, Gaziano JM, Zaharris E, MacFadyen J, Danielson E, Buring JE, Manson JE: A randomized factorial trial of vitamins C and E and beta carotene in the secondary prevention of cardiovascular events in women: results from the Women's Antioxidant Cardiovascular Study. *Arch Intern Med* 167:1610–1618, 2007
- ³⁹Gaziano JM, Glynn RJ, Christen WG, Kurth T, Belanger C, MacFadyen J, Bubes V, Manson JE, Sesso HD, Buring JE. Vitamins E and C in the prevention of prostate and total cancer in men: the Physician's Health Study II randomized controlled trial. *JAMA* 301:52–62, 2009
- ⁴⁰Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C: Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. *JAMA* 297:842–857, 2007
- ⁴¹Lonn E, Bosch J, Yusuf S, Sheridan P, Pogue J, Arnold JM, Ross C, Arnold A, Sleight P, Probstfield J, Dagenais GR; HOPE and HOPE-TOO Trial Investigators: Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial. *JAMA* 293:1338–1347, 2005
- ⁴²Yeh GY, Eisenberg DM, Kaptchuk TJ, Phillips RS: Systematic review of herbs and dietary supplements for glycemic control in diabetes. *Diabetes Care* 26:1277–1294, 2003
- ⁴³Pittler MH, Ernst E: Dietary supplements for body-weight reduction: a systematic review. *Am J Clin Nutr* 79:529–536, 2004
- ⁴⁴Singh U, Jialal I: Alpha-lipoic acid supplementation and diabetes. *Nutr Rev* 66:646–657, 2008
- ⁴⁵Scott JA, King GL: Oxidative stress and antioxidant treatment in diabetes. *Ann N Y Acad Sci* 1031:204–213, 2004
- ⁴⁶Evans JL, Goldfine ID, Maddux BA, Grodsky GM: Oxidative stress and stress-activated signaling pathways: a unifying hypothesis of type 2 diabetes. *Endocr Rev* 23:599–622, 2002
- ⁴⁷Sesso HD, Buring JE, Christen WG, Kurth T, Belanger C, MacFadyen J, Bubes V, Manson JE, Glynn RJ, Gaziano JM: Vitamins E and C in the prevention of cardiovascular disease in men: the Physicians' Health Study II randomized controlled trial. *JAMA* 300:2123–2133, 2008
- ⁴⁸Lee IM, Cook NR, Gaziano JM, Gordon D, Ridker PM, Manson JE, Hennekens CH, Buring JE: Vitamin E in the primary prevention of cardiovascular disease and cancer: the Women's Health Study: a randomized controlled trial. *JAMA* 294:56–65, 2005
- ⁴⁹Institute of Medicine Food and Nutrition Board: DRI tables. Available online from http://fnic.nal.usda.gov/nal_display/index.php?info_center=4&tax_level=3&tax_subject=256&topic_id=1342&level3_id=5140

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