Select Vitamins and Minerals in the Management of Diabetes

Vitamins and minerals play diverse roles in our bodies. Initially, the nutrition community focused on the roles micronutrients play in preventing deficiency diseases such as scurvy, pellagra, and rickets. As our understanding of nutritional science grew, it became clear that nutrients act in far broader ways. We now know that micronutrients can regulate metabolism and gene expression and influence the development and progression of many chronic diseases. Eventually, we may be able to tailor nutritional recommendations to individuals' unique genetic makeup, thus increasing the potential benefit and positive outcomes of medical nutrition therapy.

MICRONUTRIENTS

Micronutrients are vitamins and minerals that our bodies require in small quantities for specific functions. They most commonly function as essential coenzymes and cofactors for metabolic reactions and thus help support basic cellular reactions (i.e., glycolysis, the citric acid cycle, lipid and amino acid metabolism) required to maintain energy production and life. Even moderate deficiencies can lead to serious disease states. Micronutrients have been investigated as potential preventive and treatment agents for both type 1 and type 2 diabetes and for common complications of diabetes.

Micronutrient requirements can be difficult to determine because many noninvasive assessment methods, such as the measurement of plasma nutrient levels, do not accurately reflect the quantities of nutrients present in functionally important nutrient pools, and many dietary assessment methods and databases are not perfectly accurate. These and other methodological concerns have limited researchers' ability to conduct well-designed, targeted studies of micronutrient supplements in individuals who are deficient and therefore most likely to benefit from supplementation. This has likely contributed to the varied results obtained in research studies of micronutrients in people with diabetes.

Other research variables that may also contribute to the lack of consensus in study results include the use of diverse populations of patients with diabetes stemming from different biochemical origins, differences in glycemic control, variations in doses and forms of micronutrients used, variable study length, lack of control for dietary contribution of micronutrients, and use of different biochemical assays and methods of analysis. We are unlikely to have conclusive data until these methodological concerns are resolved.

The American Diabetes Association (ADA) and the American Dietetic Association recommend that healthy people at low risk for nutritional deficiencies meet their nutritional requirements with natural food sources. These organizations do not generally support the use of micronutrient supplements for people with diabetes, and the supplements they do recom-
mend are the same as those recommended for the general public. The ADA does note that people who are at increased risk for micronutrient deficiencies, such as those following very-low-calorie diets, the elderly, strict vegetarians, and other special populations, may benefit from multivitamin supplements.\textsuperscript{2,3}

Current nutritional guidelines are based on Dietary Reference Intakes (DRIs). DRIs, established in 1998, expand on the previously used Recommended Dietary Allowances (RDAs). DRIs are composed of four values: the RDA, the Adequate Intake (AI), the Estimated Average Requirement (EAR), and the Tolerable Upper Intake Level (UL).

The RDA is the level of nutrient intake believed to meet the needs of nearly all healthy individuals. It is most appropriately used as a target intake goal. However, intakes that fall below the RDA are not necessarily deficient because the RDA, by definition, is significantly greater than the needs of many people. The AI is used in place of the RDA for nutrients for which we do not yet have sufficient scientific evidence to establish an RDA.

The EAR is the level of nutrient intake believed to meet the requirements of half of the healthy individuals in a given life stage or gender group. It is most appropriately used to assess the likelihood of a nutritional deficiency. Diets that fall below the EAR for a given nutrient have a ≥50% chance of being inadequate. Supporting clinical and biochemical evidence is needed to establish the presence of an actual deficiency.

The UL is the greatest level of nutrient intake for which no adverse side effects have been noted. It is based on the members of a healthy population who are most likely to experience toxicity. The UL is usually based on total daily nutrient intake from both food and supplements. It is most appropriately used to assess the level of chronic daily nutrient intake that is likely to cause significant negative side effects. (For more information on DRIs, visit the National Institutes of Health Office of Dietary Supplements Website: http://odp.od.nih.gov/ods. Full text of all the DRI documents can be accessed without charge from the National Academy Press Website: www.nap.edu.)

Vitamin and mineral supplements are regulated by the Food and Drug Administration under the 1994 Dietary Supplement Health and Education Act (DSHEA). This act provides for only minimal regulatory oversight of supplement manufacturing and processing, focusing instead on the labeling and marketing of these products.

**SELECT MICRONUTRIENTS IN DIABETES MANAGEMENT**

**Chromium**

The trace element trivalent chromium (Cr\(^{3+}\)) is required for the maintenance of normal glucose metabolism. Experimental chromium deficiency leads to impaired glucose tolerance, which improves upon the addition of chromium to the diet.\textsuperscript{5} Because there is no accurate biochemical indicator of chromium status, the determination of clinical chromium deficiency is difficult.\textsuperscript{2,5} Effects of chromium on glycemic control, dyslipidemia, weight loss, body composition, and bone density have all been studied.\textsuperscript{4,5}

The current AI for chromium is 25 \(\mu g\) for women and 35 \(\mu g\) for men. No UL has been established. Previous recommendations placed a daily intake of \(\leq 200 \mu g/\text{day}\) within a safe and adequate range. Usual dietary intakes in the United States are estimated to range between 20 and 30 \(\mu g/\text{day}\).\textsuperscript{5}

There is no evidence that people with diabetes have increased rates of deficiency, although several risk factors for micronutrient deficiencies are common in people with diabetes. These include hyperglycemia and glycosuria, low-calorie diets, and increased age. Other factors that may increase chromium requirements include pregnancy, lactation, stress, infection, physical trauma, and chronic vigorous exercise.\textsuperscript{4,5} Because chromium is a nutrient, supplements will only benefit individuals who have a deficiency.

**Mechanism of action.** Chromium appears to act by enhancing or potentiating insulin’s actions.\textsuperscript{6} No chromium-containing enzyme has been discovered, and the biologically active form of chromium is still uncertain. Chromium’s actions have been attributed to an increase in the number of insulin receptors,\textsuperscript{5} increased binding of insulin to the insulin receptor, and increased activation of the insulin receptor in the presence of insulin.\textsuperscript{6} In vitro studies using organic forms of chromium have documented altered activity of phosphotyrosine phosphatase and phosphotyrosine kinase.\textsuperscript{5,6}

**Evidence-based research.** Numerous researchers have investigated the effects of chromium supplements on glycemic control in type 2 diabetes.\textsuperscript{7–13} Type 1 diabetes,\textsuperscript{8} gestational diabetes,\textsuperscript{14} insulin resistance,\textsuperscript{15} reactive hypoglycemia,\textsuperscript{16} the elderly,\textsuperscript{17} and steroid-induced diabetes.\textsuperscript{18} Chromium has also been shown to improve various aspects of dyslipidemia in diabetic subjects.\textsuperscript{7,9,10} There are few well-controlled, well-designed studies.

The most definitive support for chromium supplementation in type 2 diabetes was provided by a 1997 randomized, double-blind, placebo-controlled study conducted in China by Anderson et al.\textsuperscript{7} One hundred and eighty subjects were randomized to placebo, 200 \(\mu g/\text{ chromium picolinate/day, or 1,000 \(\mu g/\text{ chromium picolinate/day for 4 months. HbA1c significantly declined in both groups at 4 months compared to placebo (P <0.05) (placebo 8.5%, 200 \(\mu g\) 7.5%, 1,000 \(\mu g\) 6.6%). Fasting blood glucose (FBG) levels, 2-h oral glucose tolerance test, and insulin and cholesterol levels all decreased in the high-dose-supplement group at 4 months.

The dose-dependent response and clinically significant decreases in HbA1c (decreases are similar in magnitude to those seen with many oral hypoglycemic agents) seen in this study are encouraging, although questions remain about its applicability in the United States, where ethnicity, dietary chromium intakes, and average body mass index of people with diabetes differ from those of the Chinese subjects.

Overall, the results of research studies are mixed,\textsuperscript{5} with some showing positive effects\textsuperscript{7,9,10–14} and others having clearly negative or ambiguous results.\textsuperscript{7,10,16,18} Studies using higher doses\textsuperscript{7,11,12} and more bioavailable forms of chromium\textsuperscript{7,8,11–13} have had more positive effects than those using other forms of chromium.\textsuperscript{10,16,18} Studies in which subjects were possibly consuming low-chromium diets or had other risk factors for deficiency were also more likely to show positive effects.\textsuperscript{7,11,13,14}

Research on chromium is summarized in Table 1. When evaluating these studies, one must pay particular attention to the form and dose of chromium used; the etiology of diabetes in the population studied; subjects’ duration of diabetes, ethnicity, and weight; study duration; subjects’ relative glycemic control; statistical
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<th>Ref.</th>
<th>Subjects</th>
<th>Design</th>
<th>Results</th>
<th>Notes</th>
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<tr>
<td>7</td>
<td>180 type 2&lt;br&gt;BM I 25&lt;br&gt;China&lt;br&gt;O, I, D&lt;br&gt;HbA1c 9-12%</td>
<td>RDBPCT&lt;br&gt;Cr picolinate&lt;br&gt;200 or 1,000 μg/day&lt;br&gt;4 months</td>
<td>FBG decreased (P &lt;0.05) at 4 months in the 1,000-μg group&lt;br&gt;HbA1c decreased at 2 and 4 months in the 1,000-μg group, at 4 months in the 200-μg group (placebo 8.5%, 200 μg 7.5%, 1,000 μg 6.6%, P &lt;0.05)</td>
<td>Low BMI&lt;br&gt;Clinically significant results&lt;br&gt;Dose-dependent response&lt;br&gt;Ethnicity&lt;br&gt;Dietary Cr and initial Cr status unknown</td>
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<td>12</td>
<td>833 type 2&lt;br&gt;China&lt;br&gt;O, I</td>
<td>Up to 10 months&lt;br&gt;N on-placebo-controlled follow-up&lt;br&gt;500 μg/day&lt;br&gt;Cr picolinate</td>
<td>FBG decreased from 10.0 to 8.0 mmol/l&lt;br&gt;Postprandial BG improved from 12.0 to 9.9 mmol/l&lt;br&gt;391 of 443 subjects who had reported symptoms of fatigue reported improvement; 287 of 334 reported improvement in symptoms of thirst; and 282 of 322 reported a decrease in incidence of frequent urination</td>
<td>Effects were similar after 1-10 months&lt;br&gt;Similar effects in men and women&lt;br&gt;No confirmed negative side effects of supplemental Cr&lt;br&gt;Average BMI of subjects unknown</td>
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<tr>
<td>11</td>
<td>29&lt;br&gt;Positive family history&lt;br&gt;O, I, D&lt;br&gt;BM I 33-34&lt;br&gt;Age ~45 years</td>
<td>RDBPCT&lt;br&gt;1,000 μg/day&lt;br&gt;Cr picolinate&lt;br&gt;8 months</td>
<td>Cr improved insulin sensitivity per FSIVGTT (40%) (P &lt;0.005)&lt;br&gt;No change in HbA1c or fructosamine</td>
<td>Increased risk of diabetes&lt;br&gt;~125% IBW&lt;br&gt;3-day food records to assess usual diet&lt;br&gt;M eals for 2 days before FSIVGTT provided</td>
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<td>13</td>
<td>30 GDM&lt;br&gt;Age 25-43 years&lt;br&gt;D, I</td>
<td>DBPCT&lt;br&gt;4 μg/kg/day, placebo, 8 μg/kg/day&lt;br&gt;Cr picolinate&lt;br&gt;8 weeks</td>
<td>4 μg/kg/day Cr group had decreased HbA1c from 5.6 to 5.2% (P &lt;0.05); no change in placebo or 8 μg/kg/day Cr group&lt;br&gt;4 μg/kg/day Cr group had decreased fasting insulin (P &lt;0.035) and C-peptide (P &lt;0.044) and decreased postprandial BG (P &lt;0.049), insulin (P &lt;0.005), and C-peptide (P &lt;0.033)&lt;br&gt;8 μg/kg/day Cr group had decreased fasting insulin (P &lt;0.007) and decreased postprandial BG (P &lt;0.007), insulin (P &lt;0.049), and C-peptide (P &lt;0.011)</td>
<td>Week 20-24 of gestation&lt;br&gt;Only partial randomization&lt;br&gt;4 μg/kg/day group had higher initial HbA1c; 5.6% versus 4.7% in placebo group and 5.1% in 8 μg/kg/day group.&lt;br&gt;No comment on statistical significance of differences&lt;br&gt;Average BMI of study subjects unknown</td>
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<td>10</td>
<td>25 type 2&lt;br&gt;51 CVD only&lt;br&gt;Age 63.6 years&lt;br&gt;D, O</td>
<td>RDBPCT&lt;br&gt;250 μg/day&lt;br&gt;Cr chloride&lt;br&gt;7-16 months; mean 11 months</td>
<td>No change in FBG&lt;br&gt;No change in cholesterol&lt;br&gt;Decrease of TG (P &lt;0.02) and VLDL (P &lt;0.05) and increase in HDL (P &lt;0.005) in Cr group</td>
<td>Subjects all with established CVD-M I or intermittent claudication&lt;br&gt;No adverse effects; no change in weight&lt;br&gt;HbA1c of diabetic subjects not reported</td>
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<td>16</td>
<td>24 IGT&lt;br&gt;Age 65-74 years&lt;br&gt;BM I 30&lt;br&gt;Finnish</td>
<td>DBPCT&lt;br&gt;6 months&lt;br&gt;160 μg/day&lt;br&gt;Cr-rich yeast</td>
<td>BM I decreased in Cr group (P &lt;0.05)&lt;br&gt;No significant changes in HbA1c, FBG, fasting insulin levels, 1- or 2-h postprandial insulin, or BG levels in Cr group&lt;br&gt;No significant changes in lipoprotein levels</td>
<td>Trend to lower postprandial insulin levels in Cr group attributed to weight loss</td>
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<td>9</td>
<td>28 type 2&lt;br&gt;Age 56 years&lt;br&gt;BM I 31.2</td>
<td>RDBPCT &lt;br&gt;Cr cross-over&lt;br&gt;2 months Cr&lt;br&gt;2 months washout&lt;br&gt;200 μg/day&lt;br&gt;Cr picolinate</td>
<td>No significant change in FBG, HbA1c, LDL, or HDL levels in either treatment&lt;br&gt;TG levels decreased 17.4% from 161 to 133 mg/dl (P &lt;0.05)</td>
<td>No adverse effects of Cr&lt;br&gt;All but two subjects had undetectable serum Cr levels at start&lt;br&gt;TG not particularly high to start with&lt;br&gt;Community primarily Hispanic</td>
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BG, blood glucose; Cr, Chromium; CVD, cardiovascular disease; D, use of medical nutrition or diet therapy; DBPCT, double-blind, placebo-controlled trial; FSIVGTT, frequently sampled intravenous glucose tolerance test; GDM, gestational diabetes mellitus; I, use of insulin; IBW, ideal body weight; IGT, impaired glucose tolerance; M I; myocardial infarction, O, use of oral diabetes medication; OGTT, oral glucose tolerance test; RDBPCT, randomized, double-blind, placebo-controlled trial; TG, triglycerides.
and clinical relevance of the data; and the study design (with randomized, double-blind, placebo-controlled studies that control for dietary intake preferred). Emphasis should be placed on studies conducted after 1980, when methodological limitations in measuring chromium were resolved.

**Side effects and contraindications.** The toxicity of dietary chromium (Cr+5) is believed to be low in comparison to other trace elements. Hexavalent chromium (Cr6+), a known human carcinogen, is not present in the food supply in significant quantities. The Environmental Protection Agency sets toxicity rates at intakes >1 mg/kg body weight/day.5

Cell culture studies have suggested that high doses of chromium picolinate may cause increased rates of chromosomal damage.19 It is not certain whether chromium or picolinate were responsible for these effects, which have not been seen in vivo human or animal studies.

There are case reports of renal and hepatic toxicity, rhabdomyolysis, psychiatric disturbances, and hypoglycemia with large doses of chromium.20 In many, chromium has not been unequivocally established as the sole etiological agent.

High doses of chromium have been shown to decrease zinc absorption and may compete with iron for transport on transferrin.4,19 Vitamin C and aspirin may increase chromium absorption, but in cell culture studies, vitamin C enhanced chromium's genotoxic effects.19

**Clinical application.** Accurate biochemical indices of chromium status are not available, so assessment of status and responsiveness to supplementation can only be established by a supplement trial. Positive effects should be seen within 6–12 weeks of supplementation. If clear evidence of benefit is not established, supplementation should be discontinued because chronic use of chromium may increase the risk for as-yet-unidentified toxicities.

Supplements of up to 200 µg are unlikely to be harmful, but the safety of higher doses, which have been shown to be more effective, is less certain. Chromium picolinate and chromium nicotinate appear to have increased bioactivity when compared to inorganic forms of chromium, such as chromium chloride. The ADA does not recommend chromium supplementation for people with diabetes.21

The prevalence of chromium deficiency is unknown, but consuming good sources of chromium, such as whole grains, cheese, dried beans, nuts/seeds, mushrooms, beef, wheat germ, and broccoli, will increase the likelihood of meeting nutritional recommendations. Adequate blood glucose control and decreased intake of simple sugars may reduce urinary chromium loss.4,5

Because chromium appears to increase the activity of the insulin receptor, it is logical to expect that adequate levels of insulin must also be present. Patients using chromium supplements should be cautioned about the potential for hypoglycemia, and monitoring renal function is prudent.

**Vanadium.** The trace element vanadium has not been established as an essential nutrient, and human deficiency has not been documented. Vanadium exists in several valence states, with vanadate (+4) and vanadyl (+5) forms most common in biological systems. Vanadyl sulfate and sodium metavanadate are the most common supplemental forms, but other organic vanadium compounds have been developed.

In animal models, vanadium has been shown to facilitate glucose uptake and metabolism, facilitate lipid and amino acid metabolism, improve thyroid function, enhance insulin sensitivity, and negatively affect bone and tooth development in high doses. Vanadium appears to affect several enzyme systems and has been shown to alter the rate of activity of a number of adenosine triphosphates, phosphatases, and phosphotransferases.23

**Mechanism of action.** Vanadium's chemical structure is similar to that of phosphorus, which appears to influence its biochemical actions. It may act as a phosphate analog and has been shown to alter the rate of activity of adenosine triphosphates, phosphatases, and phosphotransferases.23

Vanadium appears to affect several points in the insulin signaling pathway and may lead to upregulation of the insulin receptor and subsequent intracellular signaling pathways. Suggested effects include insulin receptor autophosphorylation, increased protein tyrosine and serine threonine kinase activity, inhibition of phosphotyrosine phosphatase activity, increased adenylyl cyclase activity, altered glucose-6-phosphatase activity, inhibition of hepatic gluconeogenesis, and increased glycogen synthesis.23,24

**Evidence-based research.** Several small trials have evaluated the use of oral vanadium supplements in diabetes. Most focused on type 2 diabetes, although animal studies suggest that vanadium also has potential benefit in type 1 diabetes.23 In subjects with type 2 diabetes, vanadium increased insulin sensitivity as assessed by euglycemic, hyperinsulinemic clamp studies in some, but not all, trials. Glucose oxidation and glycogen synthesis were increased, and hepatic glucose output was suppressed in two studies.

In type 1 diabetes, vanadium did not affect insulin sensitivity, although daily insulin doses declined.25 Supplementation decreased FBG, HbA1c, and cholesterol levels and stimulated kinase activity.

Pharmacological doses appear to have a mild effect on insulin sensitivity and glucose utilization in type 2 diabetes. Effects in animal models are stronger than in humans, and there is no information on the long-term effects in diabetes.

Research on vanadium is summarized in Table 2. When evaluating these studies, one should pay particular attention to the form of vanadium utilized, specific animal model of diabetes used or type of diabetes in humans, doses, physiological relevance of the results, length of study, and the impact on food intake and weight caused by the anorexiant effects of vanadium. It is also important to look at study design, controls, washout period, and assay methods, especially in vitro phosphorylation assays, which are notoriously difficult to conduct well.
Vanadium may enhance the activity of digoxin and anticoagulant medications. Excessive intakes may result in a green discoloration of the tongue. Limiting daily intake to <100 μg/day has been recommended.

Clinical application. There is insufficient information on the long-term effects of pharmacological doses of vanadium to recommend its use in diabetes. Chronic intake of relatively small doses could have significant adverse effects.

Researchers are working to develop forms of vanadium that are better absorbed and have fewer side effects. Good dietary sources include black pepper, dill, parsley, mushrooms, spinach, oysters, shellfish, cereals, fish, and wine.

Niacin (vitamin B₃) occurs in two forms: nicotinic acid and niacinamide. The active coenzyme forms (nicotinamide adenine dinucleotide [NAD] and NAD phosphate) are essential for the function of hundreds of enzymes and normal carbohydrate, lipid, and protein metabolism.

As a vitamin, the two compounds function similarly, but in pharmacological doses they have distinct effects. Nicotinic acid (1–3 g/day) is an effective treatment for dyslipidemia, although its use in people with diabetes has been limited because of its negative effect on glycemic control. Pharmacological doses of niacinamide are being studied for their potential benefit in the prevention and treatment of diabetes.
Nicotinamide interacts with some anticonvulsants by increasing serum concentrations. Its use is contraindicated in active liver disease and may worsen gallbladder disease, gout, peptic ulcer disease, and allergies. In animal models, high doses have caused growth retardation, but this has not been seen in human studies.

Clinical application. Nicotinamide may help to preserve residual β-cell function in people with type 1 or type 2 diabetes, but it does not lead to clinically significant improvements in metabolic control. Typical doses are 25–50 mg/kg/day. Of concern are potential negative effects on insulin release, insulin sensitivity, and growth.

Any role that nicotinamide may have in prevention of type 1 diabetes should be elucidated at the conclusion of the ENDIT study sometime after 2003. Until then, the efficacy and safety of long-term, high-dose nicotinamide supplementation are unclear. Monitoring liver enzymes and platelet function is prudent if using high-dose nicotinamide supplements. Good dietary sources of niacin include fortified grains, some cereals, meats, fish, and dried beans.

Magnesium

The mineral magnesium functions as an essential cofactor for more than 300 enzymes. It is essential for all energy-dependent transport systems, glycolysis, oxidative energy metabolism, biosynthetic reactions, normal bone metabolism, neuromuscular activity, electrolyte balance, and cell membrane stabilization. The kidney primarily regulates magnesium homeostasis.

Magnesium deficiency has been associated with hypertension, insulin resistance, glucose intolerance, dyslipidemia, increased platelet aggregation, cardiovascular disease, complications of diabetes, and complications of pregnancy. Whether poor magnesium status plays a causal role in these disorders or is simply associated with them has not been determined.

Less than 0.3% of the body's magnesium pool is found in serum, and extracellular magnesium levels do not reflect functionally important body pools. This makes assessment of magnesium status difficult. Serum magnesium is a specific, but not sensitive, indicator of magnesium deficiency; low serum magnesium levels indicate low magnesium stores, but a deficiency must be severe before serum levels decline. More sensitive assays are being developed.

Magnesium is one of the more common micronutrient deficiencies in diabetes. Magnesium levels and increased urinary magnesium losses have been documented in both type 1 and type 2 diabetic patients. Low dietary magnesium intake has been associated with increased incidence of type 2 diabetes in some, but not all, studies.

Hypomagnesemia in diabetes is most likely due to increased urinary losses. Additional risk factors include ketoacidosis, use of certain medications including digitalis and diuretics, malabsorption syndromes, congestive heart failure, myocardial infarction (MI), electrolyte disturbances, acute critical illness, alcohol abuse, and pregnancy. Low-calorie and poor-quality diets are more likely to be inadequate in magnesium. People with diabetes may have diets low in magnesium. Hypermagnesemia may occur with increased intake of type 2 diabetes in some, but not all, studies.

The RDA is 400 mg/day for men under age 30, 420 mg/day for men over age 30, 310 mg/day for women under age 30, and 320 mg/day for women over age 30. The UL is 350 mg/day as supplemental magnesium. Daily intake from food and water is not included in the UL.

Mechanism of action. The mechanisms by which magnesium affects insulin resistance, hypertension, and cardiovascular disease are unknown. However, the widespread use of magnesium in normal metabolism of macronutrients, cellular transport systems, intracellular signaling systems, platelet aggregation, vascular smooth muscle tone and contractility, electrolyte homeostasis, and phosphorylation and dephosphorylation reactions suggests that these effects are multifactorial.

Evidence-based research. Research has focused on the following areas:

- Glycemic control. An inverse relationship between plasma magnesium levels and indices of glycemic control has been noted in both type 1 and type 2 diabetes. Clinical studies evaluating the effect of supplemental magnesium on glycemic control...
are mixed, with some studies reporting improvements and others showing no improvement.44,49 and clinical magnesium deficiency is strongly associated with insulin resistance.40,41 It is not known if low magnesium levels play a role in the development of insulin resistance, are a result of insulin resistance, or are simply a coexisting condition. In vitro evidence suggests that insulin plays a role in magnesium transport, and insulin resistance has been increased insulin levels.52

### Table 3. Select Nicotinamide Clinical Trials

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<th>Ref.</th>
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<th>Design</th>
<th>Results</th>
<th>Notes</th>
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| 31   | 173 postive ICA  
Age 5–8 years  
New Zealand | Not placebo-controlled  
1,000 mg/day Nic  
Mean follow-up 7 years | Nic associated with significant decreases in the development of type 1 diabetes (P <0.008), wide confidence interval | Clinically significant decrease in incidence of diabetes: 41% of that in non-treated group |
| 30   | 55 positive ICA  
Siblings of type 1  
Age 3–12 years  
Germany | RDBPCT; DENIS trial  
1.2 g/m² body surface/day  
Slow-release Nic  
Follow-up 2–3 years | Rates of diabetes were similar in the Nic and placebo groups  
Nic decreased first-phase insulin response (40%) to glucose (P <0.03) | Trial ended early due to lack of effect of Nic (P <0.07)  
Very-high-risk group of subjects |
| 29   | 8 positive ICA  
Siblings of type 1  
Mean age 39 years | Not randomized  
Nic placebo  
2 g/day slow-release Nic  
2 weeks | Nic decreased insulin sensitivity 23.6% (P <0.02)  
Insulin sensitivity improved in most subjects after discontinued Nic  
No clear effect on acute insulin response; increased in some subjects | Subjects tested at baseline, after 2 weeks Nic, and 2 weeks after treatment  
Doses ranged from 19.1 to 40.5 mg/kg |
| 32   | Goal 422 positive ICA  
First-degree relative type 1  
Age 5–40 years | Randomized, placebo-controlled  
Mic ulcercenter/multi-country  
Goal follow-up 5 years  
1,200 mg/M²/day  
Slow-release Nic | Treatment started in 1994; results expected after 2002 | |
| 33   | 211 type 1  
Recent diagnosis  
Ages 4–48 years | Meta-analysis  
10 randomized studies, 5 placebo-controlled  
Dose 4–100 mg/kg/day  
Up to 60 months follow-up | 1 year after diagnosis, baseline C-peptide levels significantly higher in Nic group (P <0.005), placebo-controlled group (P <0.05)  
No differences in HbA1c or insulin requirements | |
| 34   | 36 type 1  
Mean age 18 years  
Recent diagnosis | Open controlled trial  
200 mg/day Nic  
4 weeks | Stimulated C-peptide levels significantly higher at 6 months (P <0.04) and 1 year (P <0.01) compared to diagnosis  
Decreased HbA1c in Nic (P <0.03) at 1 year compared to control | No difference in remission rate  
No serious side effects  
Lower insulin doses in Nic group |
| 35   | 56 type 1  
Recent diagnosis  
Mean age 18 years  
HbA1c 8.7% | DBPCT  
25 mg/kg/day  
1 year | Stimulated C-peptide levels were increased in the group of Nic-treated patients >15 years old (P <0.02)  
No other differences between Nic and placebo were seen. | |
| 36   | 74 type 1  
Recent diagnosis | Randomized, non-placebo  
25 mg/kg/day, 50 mg/kg/day  
1 year | No significant differences between the 2 groups at 1 year  
Trend toward higher insulin doses in the 50 mg/kg/day group | |
| 37   | 18 type 2  
Negative ICA  
OHA failure  
BMI <25 | Randomized, single-blind, placebo  
6 months  
1.5 g/day Nic  
1 plus Nic, 1 plus placebo, OHA plus Nic | C-peptide release increased in two groups receiving Nic compared to placebo (P <0.05)  
No difference in HbA1c, FBG, or mean daily BG between groups | |

BG, blood glucose; FBG, fasting blood glucose; DBPCT, double blind placebo controlled trial; I, use of insulin; DENIS, Deutsch Nicotinamide Intervention Study; ICA, islet cell antibodies; Nic, nicotinamide; OHA, oral hypoglycemic agent; RDBPCT, randomized, double-blind, placebo-controlled trial.
shown to decrease magnesium uptake in type 2 diabetes. Conversely, magnesium supplementation has a mild positive effect on insulin sensitivity. Animal models show decreased insulin receptor tyrosine kinase activity and decreased glucose uptake and oxidation in magnesium deficiency. Supplementation trials have primarily focused on type 2 diabetes.

- Hypertension. Observational studies indicate an inverse relationship between magnesium levels and hypertension in people with and without diabetes. Clinical trials have produced inconsistent results.

- Cardiovascular disease. Magnesium deficiency is associated with dyslipidemias, atherosclerosis, acute MI, and cardiovascular disease (CVD) and has been shown to alter platelet aggregation and activity. Most trials in type 2 diabetes have shown little effect of supplementation on lipid levels, although improvement in the magnesium status of subjects with type 1 diabetes was associated with mild improvements in triglycerides.

- Complications. Some research suggests that subjects with common microvascular complications of diabetes have lower serum magnesium levels than subjects without complications. Patients with retinopathy have been found to have lower magnesium levels than control subjects or diabetic subjects without retinopathy. Intracellular magnesium levels were lower in patients with neuropathy. In type 2 diabetic subjects, micro- and macroalbuminuria were associated with lower serum ionized magnesium levels than was normoalbuminuria.

Research on magnesium is summarized in Table 4. When evaluating these studies, one should pay particular attention to the characteristics of the population studied; the etiology of diabetes; the presence of obesity; subjects’ age, renal function, diet composition, oral hypoglycemic or insulin use, and degree of glycemic control; the dose and form of magnesium, subjects’ baseline magnesium status and response to supplementation; assessment methods; length of trial; and the study design and ability to identify causality.

**Side effects and contraindications.** Magnesium is relatively nontoxic in people with normal renal function. Chronic supplementation and use of magnesium-containing medications such as laxatives and antacids can lead to hypermagnesemia in people with impaired renal function, defined as creatinine clearance <30 ml/min. Hypermagnesemia can result in hypotension, headaches, nausea, altered cardiac function, central nervous system disorders, and death.

**Clinical application.** The ADA recommends assessment of magnesium status in patients at risk for deficiency and supplementation for documented deficiencies. Oral supplements are available in numerous forms, but some research suggests that magnesium citrate is more bioavailable. Supplements up to the UL of 350 mg/day are appropriate; intakes >500 mg/day of elemental magnesium may cause diarrhea.

Effects of supplementation on indices of magnesium status are mixed, but some research suggests that relatively high doses of magnesium for 1-3 months followed by lower daily supplements are needed to restore and maintain magnesium in people with diabetes.

In patients with renal insufficiency, supplementation must be monitored closely. Adequate dietary intakes and good glycemic control should be encouraged to prevent deficiency. Good dietary sources include whole grains, leafy green vegetables, legumes, nuts, and fish. Diets high in saturated fat, fructose, caffeine, and alcohol may increase magnesium needs.

**Vitamin E**

This essential fat-soluble vitamin functions primarily as an antioxidant. Free radical damage is believed to play a role in many diseases, such as CVD and cancer, as well as in normal cellular aging. Antioxidants have been proposed as preventive and treatment agents for these conditions.

Low levels of vitamin E are associated with increased incidence of diabetes, and some research suggests that people with diabetes have decreased levels of antioxidants. People with diabetes may also have greater antioxidant requirements because of increased free radical production with hyperglycemia.

Increased levels of oxidative stress markers have been documented in people with diabetes, improvement in glycemic control decreases markers of oxidative stress, as does vitamin E supplementation.

Clinical trials involving people with diabetes have investigated the effect of vitamin E on diabetes prevention, insulin sensitivity, glycemic control, protein glycation, microvascular complications of diabetes, and cardiovascular disease and its risk factors.

**Mechanism of action.** Vitamin E is a potent lipophilic antioxidant. It acts to neutralize free radical species produced during normal cellular metabolism, protecting cellular membranes and lipoproteins—LDL in particular—from oxidative damage. It also interacts with water-soluble antioxidants such as glutathione. It may play a role in preventing and treating common complications of diabetes, such as CVD, nephropathy, and neuropathy, by decreasing protein glycation, lipid oxidation, and inhibition of platelet adhesion and aggregation.

**Evidence-based research.** Studies have focused on the following areas:

- CVD. People with diabetes are at increased risk for CVD. Dietary vitamin E has been associated with decreased incidence of CVD and cancer, as well as in normal cellular aging. Antioxidants have been proposed as preventive and treatment agents for these conditions.

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Vitamin E refers to a group of compounds that includes tocopherols and tocotrienols. Alpha-tocopherol is the most abundant and biologically active. Usual dietary intakes are estimated at 7-11 mg/day. The RDA for alpha-tocopherol is 15 mg/day for people 15 years of age and older. The UL for alpha-tocopherol is 1,000 mg/day from supplemental sources. Natural vitamin E (d-alpha tocopherol) has approximately twice the bioactivity of synthetic forms of the vitamin (dl-alpha tocopherol).

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Table 4. Select Magnesium Clinical Trials

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Subjects</th>
<th>Design</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>51</td>
<td>50 type 2, Netherlands; I, BM 128; HbA1c 8.7%</td>
<td>RDBPCT, 15 mmol/day; Oral MgAspHCl, 3 months; Intention to treat and on-treatment</td>
<td>Mg supplementation slightly increased plasma Mg levels (P &lt; 0.05); no change in RBC Mg, which was not low; N o change in FBG, HbA1c</td>
<td>Increased plasma Mg irrespective of group was associated with a decrease in diastolic BP; N o side effects noted; 16 drop-outs</td>
</tr>
<tr>
<td>44</td>
<td>128 type 2, Brazil; HbA1c &gt;8%</td>
<td>RDBPCT, Oral Mg oxide, 20.7 mmol/day; 41.4 mmol/day, placebo; 30 days; Intention to treat</td>
<td>Subjects with diabetes had decreased intramonomonuclear Mg (P &lt; 0.05) but not plasma Mg; N o correlation between intramonomonuclear Mg and glycemic control; 41.4 mmol Mg increased plasma Mg and decreased fructosamine levels (P &lt; 0.05); Subjects with peripheral neuropathy (P &lt; 0.05) and CVD (P &lt; 0.05) had lower intramonomonuclear Mg levels than those with diabetes but no complications or retinopathy</td>
<td>GI side effects: diarrhea, abdominal pain, nausea; N o correlation between plasma and intracellular Mg; 29 subjects did not follow protocol; N o change in weight</td>
</tr>
<tr>
<td>45</td>
<td>40 type 2, Austria; D plus O, M</td>
<td>RDBPCT, Oral Mg, 30 mmol/day; 3 months</td>
<td>Plasma Mg in diabetes significantly lower than in healthy controls (P &lt; 0.0001); Mg increased plasma Mg to levels similar to control group at 3 months; N o change in HbA1c; 7.4% pre-Mg, 7.2% post-Mg; no change in basal or OGTT insulin levels or BG levels; N o change in lipids levels</td>
<td>6 month follow-up found Mg levels declined to pre-Mg levels; 2 months of treatment did not increase plasma Mg; Diet questionnaire to assess Mg intake</td>
</tr>
<tr>
<td>53</td>
<td>9 type 2, BM 128; Mean age 73 years; D, HbA1c ?</td>
<td>RDBPCT crossover treatment, 4-week treatment; 4-week washout; 15.8 mmol/day; Oral Mg pildolate</td>
<td>M g increased plasma and RBC Mg (both P &lt; 0.001); FBG did not change; Euglycemic hyperinsulinaemic clamp increased insulin-mediated glucose disposal (P &lt; 0.005), total body glucose disposal (P &lt; 0.005), and glucose oxidation (P &lt; 0.01)</td>
<td>Subjects with peripheral neuropathy (P &lt; 0.05) and CVD (P &lt; 0.05) had lower intramonomonuclear Mg levels than those with diabetes but no complications or retinopathy; Subjects with peripheral neuropathy (P &lt; 0.05) and CVD (P &lt; 0.05) had lower intramonomonuclear Mg levels than those with diabetes but no complications or retinopathy</td>
</tr>
<tr>
<td>50</td>
<td>56 type 2, Italy; Age 64±8 years; D, O, I, BM 1—25; HbA1c 7.3%</td>
<td>RDBPCT, 15 mmol/day; Mg lactate citrate, 4 months</td>
<td>N o effect of Mg on HbA1c, FBG, lipids, renal function, or blood pressure</td>
<td>All subjects had normal plasma Mg initially</td>
</tr>
<tr>
<td>49</td>
<td>8 type 2, Italy; Age 72 years; 133% IBW; HbA1c ?</td>
<td>RPDCT crossover treatment, 4-week treatment; 2-week washout; 2 g/day; Oral Mg</td>
<td>M g increased plasma (P &lt; 0.05) and RBC Mg (P &lt; 0.01) levels; M g decreased FBG (P &lt; 0.05); Euglycemic hyperinsulinaemic clamp: M g increased acute insulin response to glucose pulse (P &lt; 0.05), glucose infusion rate (P &lt; 0.025)</td>
<td>Oral medications discontinued 3 weeks before study; Diet Mg estimated at 317 mg/day</td>
</tr>
</tbody>
</table>

BG, blood glucose; BP, blood pressure; D, use of medical nutrition or diet therapy; FBG, fasting blood glucose; GI, gastrointestinal; I, use of insulin; IBW, ideal body weight; M, metformin; Mg, magnesium; MgAspHCl, magnesium aspartate hydrochloride; O, use of oral diabetes medication; OGTT, oral glucose tolerance test; RBC, red blood cell; RDBPCT, randomized, double-blind, placebo-controlled trial; RPDCT, randomized, placebo-controlled trial.

on lipid levels or lipid oxidation have been noted in some, but not other, studies. Improvements have been noted in cell adhesion, platelet aggregation, monocyte proatherogenic activity, and endothelial function. Vitamin E has improved LDL oxidation, but positive effects may be greater for buoyant LDL than for the highly atherogenic dense LDL.

• Microvascular complications. Limited research suggests that vitamin E may be beneficial in preventing or treating microvascular complications of diabetes.

• Insulin resistance and glycemic control. Some studies have documented improvements in glycemic control and insulin resistance with vitamin E supplementation, whereas others have noted no effect or negative effects.

Research on vitamin E is summarized in Table 5. When evaluating these studies, one should pay particular attention to the population studied, presence of preexisting CVD, type of diabetes, form and dose of vitamin E, duration of supplementation, level of glycemic control, use of a pre-study run-in period, levels of antioxidant body pools, degree of incorporation into lipoproteins, degree of protection from oxidation conferred, assay...
method for oxidative markers, effects on mortality, presence of smoking or alcohol use, and supplement use and usual diets of subjects.

**Side effects and contraindications.** Vitamin E is relatively nontoxic.\(^5\) Most long-term trials have found no negative side effects with supplementa-
tion.\(^4,79,80\)

Vitamin E has been shown to have anticoagulant properties, and patients using medications and herbal supplements known to decrease blood clotting, such as warfarin, aspirin, ginkgo biloba, garlic, and ginseng, may be at increased risk for bleeding with high-
dose supplements.\(^20\) Doses of vitamin E up to 400 IU are believed to be safe.\(^1\) Doses >800 IU may alter blood clotting, although trials that have monitored prothrombin times have noted no increases.\(^4\)

Vitamin E has been associated with increased risk of hemorrhagic stroke

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**Table 5. Select Vitamin E Clinical Trials**

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Subjects</th>
<th>Design</th>
<th>Results</th>
<th>Notes</th>
</tr>
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</table>
| 66   | • 84 type 1  
    • Age 5–35 years  
    • HbA\(_1c\) 8.9% | IM DIAB IV study  
                 Prospective trial  
                 Nonrandomized, nonplacebo  
                 15 mg/kg/day VE  
                 1 year | Conclusion: effects of VE and nicotinamide on \(\beta\)-cell preservation similar  
                 HbA\(_1c\), and insulin use decreased (\(P <0.005\)).  
                 Authors noted similar results with nonsupplement patients in past  
                 Basal and stimulated C-peptide levels remained stable over year | Patients <15 years of age had lower C-peptide than patients >15 years of age  
                 VE in 1 patient resulted in transient leucopenia  
                 Form of VE not specified |
| 69   | • 53 type 2  
    • Mexico  
    • Age 40 years  
    • BM 24  
    • HbA\(_1c\) 11.9% | RDBPCT, crossover  
                 400 mg VE  
                 2 months  
                 4-week washout | VE supplementation in poorly controlled subjects did not improve FBG, HbA\(_1c\), fructoseamine, cholesterol, LDL, HDL, TG, apo-A, apo-B | Form of VE not specified |
| 70   | • 35 type 1  
    • Age 12 years | RDBPCT  
                 100 IU dl–α VE/day  
                 3 months | M odest but significant decrease in HbA\(_1c\), 12.8 to 11.5% (\(P <0.05\))  
                 M odest but significant decrease in TG (\(P <0.03\)) | Clinical significance of results is low  
                 Hematological indices OK |
| 71   | • 25 type 2  
    • Italy  
    • Age 71 years  
    • BM 27  
    • HbA\(_1c\) 7.8% | RDBPCT, crossover  
                 900 mg/day d–α VE  
                 3 months  
                 30-day washout | Decreased FBG (\(P <0.05\)), decreased HbA\(_1c\)  
                 7.8 to 7.1% (\(P <0.05\))  
                 TG (\(P <0.02\)), LDL (\(P <0.04\)), FFA, cholesterol, apo-B (\(P <0.05\))  
                 Supplements increased plasma VE, GSSG/GSH ratio, decreased plasma oxygen production, no effect on fasting or IVGTT insulin | Subjects had no micro- or macrovascular complications  
                 Pharmacological dose |
| 72   | • 30  
    • Insulin-requiring  
    • Age ~41 years  
    • BM ~28  
    • HbA\(_1c\) ~11.5% | Group randomized, blinded  
                 Placebo 600, 1,200 mg VE/day  
                 Groups matched for age, duration, and control of diabetes  
                 2 months | Decrease in HbA\(_1c\), 11.8 to 7.8% with 1,200 mg/day (\(P <0.01\)), 11.5 to 8.9% with 600 mg/day (\(P <0.001\))  
                 N o change in fasting or mean daily BG level or response to hyperglycemic clamp  
                 VE may act in an early step of glycation, possibly glucose auto-oxidation  
                 C-peptide levels mean 0.5–0.6 nmol/l  
                 Form of VE not specified  
                 Dose-dependent effect of VE on HbA\(_1c\) | Form of VE not specified |
| 67   | • 5 type 2  
    • 10 healthy controls  
    • BM 26  
    • OHA  
    • HbA\(_1c\) 7.9% | RDBPCT, crossover  
                 900 mg/day dl–α VE  
                 4 months  
                 1-month washout | Diabetes plus VE decreased FBG (\(P <0.05\)) and HbA\(_1c\)  
                 7.9 to 7.0% (\(P <0.04\))  
                 Diabetes plus VE decreased OGTT AUC (\(P <0.03\)) and increased glucose disposal (\(P <0.02\)) and nonoxidative glucose metabolism (\(P <0.02\))  
                 Diabetes plus VE no change in basal or 2 hr OGTT insulin levels  
                 VE increased serum VE and improved oxidative and membrane viscosity and to a greater degree in diabetes  
                 dl–α VE  
                 Pharmacological dose  
                 No side effects noted | dl–α VE  
                 Pharmacological dose  
                 No side effects noted |
| 68   | • 11 type 2  
    • 9 healthy controls  
    • BM diabetes 31.6  
    • Age ~44 years  
    • D; OHA, M | Not randomized, no placebo, not blinded  
                 600 mg/day α-VE | VE decreased glucose disposal rate (\(P <0.02\)) and metabolic clearance rate of GL (\(P <0.01\))  
                 Subjects with diabetes had lower serum VE and higher MDA, TPA, and PAI-1  
                 VE increased serum VE levels, decreased TPA to control levels, decreased MDA, and resulted in no change in PAI-1  
                 d– versus dl–α VE not specified  
                 BM I control 25 | cont’d on page 143 |
(and decreased incidence of ischemic stroke) in smokers. In vitro assays suggest that vitamin E can have some oxidative activity, but this has not been shown in in vivo studies.

**Clinical application.** Good sources of vitamin E are primarily higher-fat foods, such as vegetable oils, margarines, wheat germ, seeds, and nuts. Adequate intakes for antioxidant activity may be difficult to achieve for those following low-fat diets.

Supplements containing natural (dl-alpha-tocopherol) vitamin E are more bioavailable. Doses may need to be increased as much as two times that of natural vitamin E if the synthetic form of the vitamin (dl-alpha-tocopherol) is used.

Patients using medications such as orlistat, which decrease vitamin E absorption, may require vitamin E supplements. The ADA does not recommend regular supplementation of vitamin E in people with diabetes.

### B Vitamins Involved in Homocysteine Metabolism

Hyperhomocysteinemia (H homcys) is positively correlated with coronary heart disease, cerebrovascular disease, and peripheral vascular disease. It has not been determined whether the presence of H homcys precedes or follows vascular diseases.

A recent prospective, population-based study found that H homcys is a risk factor for overall mortality in type 2 diabetic patients independent of other known risk factors. H homcys was a twofold stronger risk factor for death in diabetic patients as compared to nondiabetic patients. For each 5 μmol/l increment of homocysteine, risk of mortality rose by 17% in nondiabetic and 60% in diabetic subjects.

Adequate levels of the vitamins pyridoxine (vitamin B₆), cobalamin (vitamin B₁₂), and folate are necessary for normal homocysteine metabolism. Folate refers to a family of naturally occurring compounds. Folic acid is the synthetic form of the vitamin. Folate is an essential coenzyme for reactions involving the transfer of one-carbon-units in amino acid and nucleic acid synthesis.

The RDA for folate is 400 μg/day for adults and 600 μg per day in pregnancy. The UL is 1,000 μg/day of folic acid from supplements and does not include dietary sources. Folate is widely available in the food supply but as much as 50–95% of it may be destroyed by processing. Folic acid is the preferred supplemental form.

Conditions that increase the risk of folate deficiency include pregnancy and lactation; alcoholism; anorexia; older age; chronic use of medications such as anticonvulsants, antiproliferative drugs, and oral contraceptives; malabsorption disorders; and gastrointestinal surgery.

The biguanide metformin may reduce folate and vitamin B₁₂ absorption and increase homocysteine levels. The clinical significance of this effect is unknown. Folic acid supplements in patients using metformin decreased homocysteine levels, and calcium supplements improved serum B₁₂ levels presumably by reversing the negative effects of metformin on vitamin B₁₂ absorption.

B₁₂ has been used as a treatment for peripheral neuropathy in diabetes, but there is insufficient evidence to support this use. Many of the symptoms of B₁₂ deficiency are similar to those associated with aging and neuropathy (ataxia, memory changes). Thus, clinicians must be alert to the possibility of and specifically test for B₁₂ deficiency in these populations. Risk of vitamin B₁₂ deficiency is increased with elderly age, achlorhydria, alcohol abuse, long-term gastriac acid inhibitors, vegan diet, partial gastrectomy, celiac sprue, and autoimmune disorders including type 1 diabetes, AIDS/HIV, and thyroid disorders.

The adult RDA for B₁₂ is 2.4 μg/day. A UL has not been set, but daily doses up to 100 μg/day have not been associated with toxicity.

Risk of B₆ deficiency is increased with elderly age, alcoholism, high-protein intakes, liver disease, dialysis,
and use of medications such as corticosteroids, penicillamine, anticonvulsants, and isoniazid.\textsuperscript{1,4} Poor glycemic control may also lead to increased urinary losses.

\textit{B}_6 acts as an essential cofactor for hundreds of enzymes and plays a role in glucose, lipid, and amino acid metabolism and neurotransmitter synthesis. The active coenzyme form of the vitamin, pyridoxal 5’ phosphate, in muscle tissue is closely associated with glycoprotein phosphorylase.\textsuperscript{3} Deficiency of \textit{B}_6 in humans and animals is associated with glucose intolerance, but supplementation does not result in improved glycemic control.\textsuperscript{2} \textit{B}_6 is not an effective treatment for diabetic neuropathy.\textsuperscript{3} The RDA for \textit{B}_6 is 1.3 mg/day for adults up to the age 50.

The RDA increases to 1.5 mg/day for women and 1.7 mg/day for men over age 50. The UL for \textit{B}_6 is 100 mg/day for adults.

**Mechanism of action.** The amino acid homocysteine can be metabolized through transulfuration or remethylation. In the remethylation pathway, methionine synthase converts homocysteine to methionine using folate as the methyl donor.\textsuperscript{1,81} \textit{B}_12 acts as an essential cofactor for this reaction. In the transulfuration pathway, homocysteine and serine combine to form cystathionine. This reaction is catalyzed by cystathionine B-synthase and requires \textit{B}_6 as a coenzyme.\textsuperscript{1,81}

The mechanism by which increased homocysteine levels increase CVD risk has not been determined but is believed to result from pro-oxidant activity of the amino acid, endothelial dysfunction, and increased platelet activation.\textsuperscript{81}

**Evidence-based research.** This summary focuses on folate because it is the primary nutritional determinant of homocysteine levels. The prevalence of \textit{H}cyt may vary between 5 and 30% in the general population. \textit{H}cyt has been found in type 2 diabetes,\textsuperscript{69} and in some,\textsuperscript{68} but not all,\textsuperscript{69} studies of type 1 diabetes. Differences in renal filtration rates may explain some of the variable results seen in serum homocysteine levels in diabetes; hyperfiltration decreases homocysteine levels, and impaired filtration rates increase homocysteine levels.

Elevated plasma levels of homocysteine have been positively associated with CVD in some studies of people with diabetes.\textsuperscript{87,88} \textit{H}cyt is also associated with increased incidence of nephropathy, decreased renal function, and formation of CVD,\textsuperscript{89,90} and other microvascular complications of diabetes.\textsuperscript{88,90,91} Others have found no association between homocysteine levels and CVD,\textsuperscript{90,91} retinopathy,\textsuperscript{90} and indices of renal function\textsuperscript{92} or neuropathy.\textsuperscript{97}

It has not been determined whether the presence of \textit{H}cyt precedes or follows the development of these conditions, although impairment of renal filtration clearly contributes to \textit{H}cyt.

Elevated homocysteine levels in diabetes have also been associated with menopausal status, increased body mass index, smoking, and age.

In people without diabetes, there is an inverse correlation between serum folate and homocysteine levels, even in subjects with adequate nutrition.\textsuperscript{81} In diabetes, serum folate and homocysteine levels have been found to be inversely correlated in some,\textsuperscript{87,90} but not all,\textsuperscript{90} studies. Serum \textit{B}_12 levels\textsuperscript{90} are also inversely correlated with homocysteine levels, and serum pyridoxal 5’ phosphate (\textit{B}_6) is inversely correlated with post-methionine-load homocysteine levels.

In patients with diabetes and \textit{H}cyt, increased folate intake decreases and in some cases normalizes serum homocysteine levels.\textsuperscript{85,93} A meta-analysis found that treatment with 0.5–5 mg/day of folie acid lowers homocysteine levels by 15–40% within 6 weeks.\textsuperscript{94} Others have estimated that decreasing homocysteine levels by 5 μmol/l may reduce cardiovascular death by 10%.\textsuperscript{95} It is not known if supplementation is effective in prevention or treatment of micro- and macrovascular complications associated with \textit{H}cyt.

When evaluating research in this area, one should pay particular attention to the folate, \textit{B}_12, and \textit{B}_6 status of subjects; dose and form of folate used; effects of supplementation on folate and homocysteine levels; subjects’ age, type of diabetes, use of biguanides, duration of diabetes, menopausal status, weight, and glycemic control; presence of impaired renal function or hyperfiltration; and length of supplementation, with more than 4 weeks and possibly up to 3 months necessary for full effects. The impact of ethnicity and methyltetrahydrofolate reductase (MTHFR) gene mutation incidence could also affect results. (MTHFR is an enzyme essential for the metabolism of folate and is important in the metabolism of homocysteine. A common mutation in the MTHFR gene is associated with \textit{H}cyt in homozygous subjects.)

**Side effects and contraindications.** Doses of folate ≤15 mg/day have not been associated with adverse effects in healthy adults.\textsuperscript{4} However, folate supplementation may mask the anemia associated with \textit{B}_12 deficiency and result in permanent nerve damage.\textsuperscript{1} High-dose folate supplements may also interfere with anticonvulsant medications.\textsuperscript{1} High-dose \textit{B}_6 supplements are not recommended as a treatment for neuropathy; in fact, toxicity symptoms include neuropathy.\textsuperscript{2}

**Clinical application.** Long-term trials are needed to determine the effects of folic acid on micro- and macrovascular complications, both early and late in the disease process. Early research suggests that folate supplements decrease \textit{H}cyt levels and may be beneficial in the prevention and management of vascular complications in diabetes. Folic acid supplements are recommended for all women of childbearing age.

The primary risk of supplementation relates to the potential for undiagnosed \textit{B}_12 deficiency. Since impaired \textit{B}_12 absorption is estimated to occur in 10–30% of people over the age of 50, assessment of \textit{B}_12 status in patients with peripheral neuropathy is prudent. In elderly people with achlorhydria, synthetic forms of oral \textit{B}_12 supplements are better absorbed than food-bound \textit{B}_12 and are therefore preferred. The use of biguanides may decrease folate and \textit{B}_12 absorption.

All patients with diabetes should be encouraged to consume adequate quantities of dietary folate, \textit{B}_12, and \textit{B}_6 to modify factors such as alcohol intake and smoking, which increase homocysteine levels. All “enriched” cereal grain products (rice, flour, breakfast cereals, pasta, bread) in the United States have been fortified with folic acid since 1998. Good dietary sources of folate include fortified grain and cereal products, spinach, orange juice, strawberries, and peanuts.\textsuperscript{4} Good dietary sources of \textit{B}_12 are animal products, and good sources of \textit{B}_6 include whole grains, animal products, and legumes.\textsuperscript{4}

**SUMMARY**

As health care providers interested in promoting the optimal health of people with diabetes, we need to act as an unbiased resource on the numerous
treatments available to our patients. We need to be open to new treatment regimens while also serving as careful watchdogs for ineffective or dangerous therapies. Above all, we need to encourage our patients’ involvement in and ownership of their diabetes, and help them to focus their efforts where they are likely to receive the greatest benefits. In the future, this will likely include nutritional supplements for people whom research has identified as having the genetic or clinical potential to benefit from them.

References


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