



Dietary Supplements and Probiotics for Diabetes

An overview of the most popular alternative therapeutic modalities.

According to recently published National Health and Nutrition Examination Study data from 2003 to 2006, approximately half of all Americans use supplements,¹ and according to the National Center for Health Statistics, we spend about \$14.8 billion on supplements annually.² But studies provide varying information on exactly how many people use supplements and don't reveal the specifics of dosing, which products are being used, or even which botanical parts are being used. Less clear is exactly who is using them and for what reasons. According to one evaluation, only 33.4% of supplement users inform their conventional health care provider (as opposed to providers of alternative care modalities) about supplement use.³ Patients with diabetes, for instance, may use such products with certain goals in mind; a discussion of the products used most often by diabetes patients—including cinnamon, coenzyme Q10 (CoQ10), hibiscus, magnesium, mulberry, vinegar, and probiotics—can be helpful to clinicians who care for them.

Supplement and probiotic use in diabetes patients. An evaluation of the 2002 National Health Interview Survey indicated that 22% of diabetes patients use herbal products.⁴ A different survey of adult patients with diabetes found that 67% were using some type of vitamin or supplement.⁴ A recent review of the medication histories of 459 individuals with diabetes indicated that 55% use some type of supplement on a daily basis.⁵ Although information on why patients with diabetes choose to take supplements is incomplete, it's likely that rising costs of medications and provider visits are important factors.⁵ Other possibilities are a desire to avoid adverse effects associated with conventional medications, limitations in the ability of conventional treatments to cure health problems, a belief that because supplements are “natural” they must be safe, and the influence of friends and coworkers who suggest that supplements may help.⁶

It's important for clinicians to recognize that these products, despite being “natural,” have active



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chemical constituents with pharmacologic activity and that adverse effects and drug interactions are very real possibilities. However, there's a great amount of research in progress, and it's important for clinicians to stay informed. It's also important for clinicians to be respectful of patients' desires to use supplements; just as clinicians should always ask patients which medications they're taking, they should ask about supplement use.

Beginning the conversation. Clinicians should ask their patients what they hope to achieve with supplement use—likely possibilities include a desire to lower their blood glucose concentration, glycated hemoglobin (HbA_{1c}) level, blood pressure, or cholesterol level. If a patient has used a product for a significant length of time, the clinician can help the patient to figure out whether it's helping her or him achieve that objective. Most important, the clinician should also encourage patients not to discontinue their conventional medications. Because there are many safety issues involved, patients should be carefully monitored, especially because these products aren't approved for the treatment of disease and



Table 1. Dietary Supplements Used in Diabetes

Product	Chemical Constituents	Mechanisms of Action	Adverse Effects	Drug Interactions
Cinnamon ^{7,8}	Procyanidin	Enhances insulin action Increases glucose uptake, decreases glycogen synthesis Increases phosphorylation of insulin receptors May aid in triggering insulin cascade system May help delay gastric emptying and reduce excess postprandial glucose and triglyceride levels	Topical allergic reactions Possible bleeding	Possible hypoglycemia if combined with secretagogues Possible bleeding if combined with blood thinners because of coumarin content
CoQ10 ^{7,10,11}	10-carbon side chain with structure similar to vitamin K	Antioxidant Increases adenosine triphosphate production Scavenges oxygen free radicals Membrane stabilizer	No serious effects with long-term use Gastrointestinal upset Insomnia Increased transaminase levels	Warfarin (Coumadin): may decrease international normalized ratio Antihypertensives: may have additive blood pressure–lowering effects when combined with antihypertensives Statins: may protect against statin-induced myopathy Adriamycin: may decrease cardiac toxicity
Hibiscus ^{7,12,13}	Anthocyanins: delphinidin-3-sambubioside, cyanidin-3-sambubioside	Angiotensin-converting enzyme (ACE) inhibition Vasorelaxation (possibly through calcium channels) Diuresis	Bitter taste No major problems with liver or renal function in short-term trials	Acetaminophen with diclofenac: decreased elimination half-life ACE inhibitors and other antihypertensives: possible additive hypotensive effects
Magnesium ^{7,14-16}	Numerous salt forms: sulfate, citrate, hydroxide, oxide, chloride	A cofactor for enzymes in glucose metabolic pathways and phosphorylation reactions Low dietary intake may contribute to insulin resistance and decreased insulin action	Gastrointestinal upset Magnesium accumulation in renal disease	Magnesium depleters: diuretics, steroids, digoxin, β_2 agonists Impaired absorption of certain antibiotics, calcium, bisphosphonates Hypotension with calcium channel blockers Hypermagnesemia with potassium-sparing diuretics

Table 1. Continued

<p>Mulberry^{17, 18}</p>	<p>1-deoxynojirimycin Fagomine Antioxidants Resveratrol in leaves</p>	<p>Alpha glucosidase inhibition Insulin secretion Decreased lipid peroxidation</p>	<p>Possible gastro-intestinal upset (theoretically, as a result of alpha glucosidase inhibition)</p>	<p>Additive blood glucose lowering with hypoglycemic agents (theoretically, as a result of alpha glucosidase inhibition)</p>
<p>Vinegar¹⁹⁻²⁵</p>	<p>Acetic acid</p>	<p>May delay gastric emptying May block disaccharide (but not monosaccharide) activity and block complete digestion of starches May help promote muscle glucose uptake May alter glycolysis–hepatic gluconeogenesis cycle Increased satiety</p>	<p>Gastrointestinal upset Possible hypokalemia Possible hypoglycemia in patients with gastroparesis Osteoporosis</p>	<p>Possible effect on drug absorption Case report of hypokalemia with large amounts (toxicity is therefore possible in combination with drugs for which hypokalemia may pose a risk, such as digoxin) Possible hypoglycemia with secretagogues</p>

lack long-term, clinical trials to support their use. A discussion of some of the products currently preferred by diabetes patients—cinnamon, CoQ10, hibiscus, magnesium, mulberry, vinegar, and probiotics—can be of help to today’s clinicians.

SUPPLEMENTS

Further information on these products, including their chemical constituents, possible mechanisms of action, adverse effects, and drug interactions, can be found in Table 1.⁷⁻²⁵

Cinnamon (*Cinnamomum cassia*). Cinnamon is commonly used as a natural treatment for diabetes and hyperlipidemia and, overall, probably has more benefits than drawbacks. A meta-analysis of five clinical trials involving a total of 282 people with diabetes (type 1 in adolescents and type 2 in adults) indicated that dosages of 1 to 6 g/day of cassia cinnamon didn’t result in significant decreases in HbA_{1c}, fasting glucose, or lipid levels.²⁶ Another trial, a three-month study in 102 patients with type 2 diabetes, found a statistically significant decrease in HbA_{1c} of 0.83% using a dosage of 1 g/day.²⁷ An even smaller study, of 58 people with type 2 diabetes who were taking 2 g/day, showed a small but significant decrease in HbA_{1c} of 0.36%.²⁸

CoQ10. CoQ10 is a provitamin (a vitamin precursor that’s converted to a vitamin during metabolism) and one of the supplements most commonly used by people, regardless of diabetes status. A deficiency in

CoQ10 is thought to be present in many diseases, including diabetes.¹⁰ CoQ10 has been used to aid in treating a variety of cardiovascular diseases, including hypertension, heart failure, angina, and statin-induced myopathy, among others.^{10, 11, 29} Although its exact role in diabetes is unknown, CoQ10 has demonstrated long-term safety.

In combination with fenofibrate, CoQ10 has demonstrated statistically significant improvements in blood pressure and glucose control in patients with type 2 diabetes.

CoQ10 has also demonstrated nonsignificant declines in mean glucose (from 8.9 to 8.06 mmol/L, or 160 to 145 mg/dL) in patients with type 1 diabetes.³⁰ In combination with fenofibrate, CoQ10 has demonstrated statistically significant improvements in blood pressure and glucose control in patients with type 2 diabetes (the HbA_{1c} level decreased from 7.5% to 7.2%; systolic blood pressure decreased by 6.1 mm Hg; and the diastolic pressure decreased by 2.9 mm Hg).³¹ One of the main reasons CoQ10 is used in diabetes is because of its positive effects on endothelial function.³²



Hibiscus (*Hibiscus sabdariffa* L.). Hibiscus is a shrub that bears brightly colored blooms. A tea made from the flower is used to treat hypertension and hyperlipidemia in patients with and without diabetes. Hibiscus is known by a variety of names, including hibiscus tea, roselle, agua de Jamaica, and sour tea, among others.¹² Hibiscus flowers and tea sachets steeped in water have blood pressure–lowering effects, although they’re not as great as those of angiotensin-converting enzyme inhibitors.³³ Overall, the benefits of hibiscus are seen mainly in the treatment of mild hypertension.

In patients with type 2 diabetes, hibiscus has been shown to significantly decrease systolic blood pressure (from 134.4 to 112.7 mm Hg)³⁴ and low-density lipoprotein (LDL) cholesterol (from 137.5 to 128.5 mg/dL).³⁵ Clinicians should ask patients about their use of specific teas or other products, in case they’re using hibiscus.

diabetes compared mulberry with a sulfonylurea. Mulberry significantly decreased fasting glucose levels (from 153 to 110 mg/dL), LDL cholesterol and triglyceride levels, and significantly increased high-density lipoprotein cholesterol levels.³⁹ In a very small study, mulberry leaf combined with propolis demonstrated significant lowering of the blood glucose level from 202 to 129 mg/dL, and the mean HbA_{1c} level decreased from 7.8% to 7%.⁴⁰ The plant’s overall benefit may be the result of diminished carbohydrate absorption.

Vinegar. Acetic acid is the main constituent of vinegar, and many people have been interested in adding vinegar to their diet to benefit their health. Some of the adverse effects listed in Table 1 are theoretical because only preliminary information on vinegar’s adverse effects is available, and that mainly involves gastrointestinal effects.²² That said, hypoglycemia in patients with type 1 diabetes and

A meta-analysis of randomized controlled trials evaluating magnesium supplementation showed a significant decrease in fasting glucose levels of 10 mg/dL and a nonsignificant decrease in HbA_{1c}.

Magnesium. Magnesium is a mineral found in many foods that serves as an enzyme cofactor in various glucose metabolic pathways. Many diabetes patients don’t consume sufficient amounts of magnesium-containing foods to derive benefit, however. Magnesium-rich foods should be encouraged, but supplements should be used with caution in patients at risk for renal disease or drug interactions. Benefits obtained from magnesium supplementation vary, depending on the study. One study found that 100 mg/day of magnesium intake significantly decreased the risk of developing diabetes.³⁶ In another study, overweight, insulin-resistant patients taking magnesium supplements experienced improved insulin sensitivity and decreased fasting glucose levels.³⁷ And a meta-analysis of randomized controlled trials evaluating magnesium supplementation showed a significant decrease in fasting glucose levels of 10 mg/dL and a nonsignificant decrease in HbA_{1c}.³⁸

Mulberry (*Morus alba*). Mulberry-leaf tea and extract have been widely used in Asia for diabetes. Mulberry-leaf is used in combination with other teas. A small 30-day study in patients with type 2

gastroparesis has been reported.²³ The possible drug interactions listed, too, are mainly theoretical and are based on a case report and mechanism proposed by the authors of the report.²⁴

In one small study involving patients with type 1 diabetes, vinegar use decreased postprandial glucose levels by 20% after a standardized meal.²⁵ In a study comprising four subtrials, approximately 2 t of vinegar taken with meals also decreased postprandial glucose by about 20% in healthy adults.⁴¹ Another small trial showed that vinegar resulted in a small decrease in HbA_{1c} in patients with type 2 diabetes,²⁰ and some authors have suggested that as little as 2 t of vinegar used in a salad, for instance, may attenuate increases in postprandial glucose.⁴¹

PROBIOTICS

To discuss probiotics, background information on the microbiota is necessary. Millions to trillions of microbial organisms in the gut constitute what is known as the human microbiota.⁴² The role of microbiota in various disease states has been widely studied, and associations of different bacterial populations with obesity, insulin resistance, and diabetes

Table 2. Characteristics of Probiotics Used by Patients with Diabetes⁵¹⁻⁵³

Mechanisms of Action	Adverse Effects	Drug Interactions
Compete with pathogenic microbes for intestinal epithelial receptors	Bloating, flatulence (subside with continued use)	Antibiotics (must separate administration by 2 hrs)
Release beneficial antimicrobial compounds that combat pathogenic microbes, including organic acids (such as lactic, acetic, and propionic acid), hydrogen peroxide, free fatty acids, bacteriocins	<i>Saccharomyces boulardii</i> : constipation and increased thirst (rare)	<i>S. boulardii</i> may interact with oral antifungals or in patients with yeast allergy, thereby decreasing efficacy of the probiotic
Increase mucin secretion, so probiotics bind to intestinal mucosa and block the binding of pathogens to the intestinal mucosa	May migrate from gastrointestinal tract into the bloodstream and cause problems	Immunosuppressants: probiotics may cause pathogenic colonization or infection in immunocompromised patients
Modify and block toxins	Transfer of antibiotic resistance to pathogenic bacteria (theoretically)	
Stimulate host immunity by stimulating certain interferons and interleukins and altering cytokine profiles		
Stabilize and enhance the epithelial intestinal barrier		
"Prime" gut-associated lymphoid tissue (an important immunomodulator)		

are coming to light. The microbiota has been described as a "microbial organ" that plays a role in many different host processes, "including defense against pathogens at the gut level" and various disease states.⁴²

Microbiota in obesity and diabetes. Alterations in the gut microbiota may involve suppressed production of beneficial gut hormones such as glucagon-like peptide-1 (GLP-1), increased triglyceride production,⁴³ inflammation,⁴⁴ inhibition of insulin signaling, and changes in energy flux.^{43,44} GLP-1 is produced in the digestive tract and is involved with, among other processes, promoting satiety and lowering glucose levels (through the stimulation of pancreatic insulin and suppression of glucagon).⁴³

Because certain microbiota may be associated with inflammation and obesity, two questions then arise: can microbiota be modified to diminish some of the harmful effects of inflammation and obesity, and (if so) how should that be done? Certain substances may help modify microbiota: prebiotics, probiotics, or a combination of the two (symbiotics). Prebiotics are nondigestible food components that benefit a host organism by stimulating growth or activity of one or more gut bacteria.⁴⁵ Probiotics are "live microorganisms that are administered orally and allow colonic colonization and confer a host health benefit."⁴⁶

Examples of prebiotics include fructooligosaccharides, psyllium, and polydextrose. They're found in many foods, such as whole grains, garlic, honey, onions, and leeks. Fructooligosaccharides stimulate

the growth of beneficial bacteria such as *Bifidobacterium* and *Lactobacillus*. In animals, fructooligosaccharide supplementation is associated with increased GLP-1 levels⁴⁷ and, possibly, enhanced production of glucagon-like peptide-2, a proglucagon-derived peptide that stimulates intestinal glucose transport and decreases gut permeability.⁴⁴

Immunocompromised patients, postsurgical patients, and patients undergoing chemotherapy or radiation aren't appropriate candidates for probiotic use.

Studies of probiotics in diabetes are emerging. One suggested that probiotics enhanced insulin sensitivity in type 2 diabetes.⁴⁸ In another study, probiotic use during pregnancy resulted in fewer cases of gestational diabetes.⁴⁹ However, before clinicians universally recommend probiotics, it's important to consider that there are serious safety concerns. For instance, probiotic use in patients with acute pancreatitis has resulted in higher mortality.⁵⁰ Also, there have been rare cases of infections and other adverse consequences, primarily in immunocompromised



patients.^{50,51} It's likely, therefore, that immunocompromised patients, postsurgical patients, and patients undergoing chemotherapy or radiation are especially vulnerable and aren't appropriate candidates for probiotic use.

The use of probiotics requires careful consideration of both their source and formulation. They're available in foods and as supplements (as pills, drinks, and powders and in yogurt, for instance), and none has been shown to be clearly superior to the others. Commonly used probiotics include *Lactobacillus* species, *Bifidobacterium* species, *Saccharomyces boulardii*, *Streptococcus thermophilus*, and *Bacillus cereus*, among others. There is a popular brand, VSL#3, that combines species from three different genera: one species of *S. thermophilus*, three species of *Bifidobacterium*, and four species of *Lactobacillus*.⁴² Although the extent of their pharmacologic effects is unknown, probiotics have many possible mechanisms of action, adverse effects, and possible drug interactions; see Table 2⁵¹⁻⁵³ for more.

IN SUM

The most important message for the clinical nurse to take away from this discussion is that patients with diabetes may take dietary supplements—for a variety of reasons—and nurses should be prepared to provide information and guidance as part of routine patient care. ▼

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