

## Diabetes

The consequences of uncontrolled diabetes are severe: blindness, kidney failure, increased risk of heart disease, and painful peripheral nerve damage. Today, most practitioners focus treatment on strict blood sugar control. While diabetes is characterized by excess blood glucose (the form of sugar used by cells as energy), this simplified approach can actually hasten the progression of the most common form of diabetes and does nothing to address the damage it causes.

A new approach to diabetes recognition and treatment is needed because the conventional wisdom has failed us. America is in the midst of a diabetes epidemic. Over the past 20 years, the number of adults diagnosed with diabetes has more than doubled, and children are being diagnosed with diabetes in alarming numbers. Diabetes has rapidly emerged as a leading culprit in the epidemic of heart disease that is sweeping the country, and it is a leading cause of amputation and blindness among adults.

It is crucial that diabetics (and those predisposed to diabetes) understand the ways in which blood glucose causes damage and take active steps to interrupt these processes. The most notorious process is glycation, the same process that causes food to brown in an oven. Glycation (defined as sugar molecules reacting with proteins to produce nonfunctional structures in the body) is a key feature of diabetes-related complications because it compromises proteins throughout the body and is linked to nerve damage, heart attack, and blindness.

Oxidative stress is also central to the damage caused by diabetes. Diabetics suffer from high levels of free radicals that damage arteries throughout the body, from the eyes to the heart. Once again, it is important that diabetics understand their need for antioxidant therapy to help reduce oxidative stress and lower the risk of diabetic complications.

### THE DIFFERENCE BETWEEN TYPE 1 AND TYPE 2 DIABETES

There are two types of diabetes: type 1 and type 2. Underlying either form of diabetes is a disorder of insulin production, use, or both. Insulin is a hormone responsible for transporting glucose into cells. When there is excess glucose in the blood, insulin is secreted from the pancreas and signals the liver and muscles to store glucose as glycogen. Insulin also stimulates adipose tissue to store glucose as fat for long-term energy reserves. Insulin receptors are found in all cells throughout the body. In a healthy person, blood glucose levels are extremely stable (Kumar V et al 2005). Normal fasting glucose levels range between 70 and 100 mg/dL.

**Type 1 diabetes.** Type 1 diabetes, formerly known as insulin-dependent diabetes, is an autoimmune condition that occurs when the body attacks and destroys the cells (called beta cells) that make insulin. Type 1 diabetes accounts for about 5 to 10 percent of cases. Because type 1 diabetics can no longer make insulin, insulin replacement therapy is essential.

**Type 2 diabetes.** Type 2 diabetes, formerly known as non-insulin-dependent diabetes, occurs when the body is no longer able to use insulin effectively and gradually becomes resistant to its effects. It is a slowly progressing disease that goes through identifiable stages. In the early stages of diabetes, both insulin and glucose levels are elevated (conditions called hyperinsulinemia and hyperglycemia, respectively). In the later stages, insulin levels are reduced, and blood glucose levels are very elevated. Although few people are aware of this crucial distinction, therapy for type 2 diabetes should be tailored to the stage of the disease.

Risk factors for type 2 diabetes include aging, obesity, family history, physical inactivity, ethnicity, and impaired glucose metabolism. Type 2 diabetes is also a prominent risk of metabolic syndrome, a constellation of conditions that includes insulin resistance along with hypertension, lipid disorders, and overweight. For details, see the chapter titled Metabolic Syndrome.

### THE DIABETES DAMAGE CASCADE

Glycation and oxidative stress are central to the damage caused by diabetes. Unfortunately, neither of them figures into conventional treatment for diabetes, which is generally concerned only with blood sugar control.

Glycation occurs when glucose reacts with protein, resulting in sugar-damaged proteins called advanced glycation end products (AGEs) (Kohn RR et al 1984; Monnier VM et al 1984). One well-known AGE among diabetics is glycated hemoglobin (HbA1c). HbA1c is created when glucose molecules bind to hemoglobin in the blood. Measuring HbA1c in the blood can help determine the overall exposure of hemoglobin to glucose, which yields a picture of long-term blood glucose levels.

Glycated proteins cause damage to cells in numerous ways, including impairing cellular function, which induces the production of

inflammatory cytokines (Wright E Jr. et al 2006) and free radicals (Forbes JM et al 2003; Schmidt AM et al 2000). In animal studies, inhibiting glycation protects against damage to the kidney, nerves, and eyes (Forbes JM et al 2003; Sakurai S et al 2003). In a large human trial, therapies that resulted in each 1 percent reduction in HbA1c correlated with a 21 percent reduction in risk for any complication of diabetes, a 21 percent reduction in deaths related to diabetes, a 14 percent reduction in heart attack, and a 37 percent reduction in microvascular complications (Stratton IM et al 2000).

High levels of blood glucose and glycation also produce free radicals that further damage cellular proteins (Vincent AM et al 2005) and reduce nitric oxide levels. Nitric oxide is a potent vasodilator that helps keep arteries relaxed and wide open. Oxidative stress in diabetes is also linked to endothelial dysfunction, the process that characterizes atherosclerotic heart disease. According to studies, diabetes encourages white blood cells to stick to the endothelium, or the thin layer of cells that line the inside of arteries. These white blood cells cause the local release of pro-inflammatory chemicals that damage the endothelium, accelerating atherosclerosis (Lum H et al 2001). Diabetes is closely associated with severe coronary heart disease and increased risk of heart attack.

## **SYMPTOMS AND DIAGNOSIS OF DIABETES**

Common symptoms of diabetes include increased thirst and urination, unusual weight changes, irritability, fatigue, and blurry vision. Clinical abnormalities include hyperglycemia and glucose in the urine. The breath might smell sweet because of ketones in the blood (ketosis), which are naturally sweet smelling. Dark outgrowths of skin (skin tags) may also appear.

The most common clinical tests used to diagnose diabetes are measures of blood glucose. The common fasting glucose test measures the amount of glucose in the blood after fasting. Prediabetes is diagnosed if the fasting blood glucose level is between 100 and 125 mg/dL. Diabetes is diagnosed if the fasting blood glucose level rises to 126 mg/dL or above.

The glucose tolerance test is used to measure insulin response to high glucose levels. During this test, patients are given glucose, and the rise in blood glucose levels is measured. Prediabetes is diagnosed if the glucose level rises to between 140 and 199 mg/dL. Diabetes is diagnosed if blood glucose levels rise to 200 mg/dL or higher.

The HbA1c test is also helpful in diagnosing less severe cases of diabetes. From this test clinicians can estimate the average blood glucose level during the preceding two to four months. Normally 4 to 6 percent of hemoglobin is glycosylated, which corresponds to average blood glucose between 60 and 120 mg/dL. Mild hyperglycemia increases HbA1c to 8 to 10 percent (or 180 to 240 mg/dL), while severe hyperglycemia increases HbA1c values up to 20 percent. For diabetics, a healthy HbA1c level is less than 7 percent, which corresponds to an average blood glucose level of 150 mg/dL or less.

## **THE TRUTH ABOUT TYPE 2 DIABETES THERAPY**

Before discussing therapy for type 2 diabetes, it is important to understand the logic behind conventional therapy—and to understand why this logic is flawed. Type 2 diabetics are routinely told they need to boost their levels of insulin, which will help drive blood glucose into their cells and lower their blood glucose levels. Unfortunately, this assumption defies common sense.

In the early stages of type 2 diabetes, insulin levels are already elevated (hyperinsulinemia). This is because the problem isn't with insulin production; rather, the underlying defect in type 2 diabetes is a metabolic defect of insulin utilization. The delicate insulin receptors on cell membranes are less responsive to the insulin than are the insulin receptors of people without type 2 diabetes, which means that less glucose is absorbed from the blood stream than would be normally, and glucose levels slowly rise.

This elevation in glucose upsets the body's natural balance, prompting the pancreas to discharge copious amounts of insulin to normalize glucose levels. This short-term, biological fix successfully drives glucose into cells, thereby lowering blood glucose levels, but it also hastens the disease's progress. Eventually, the fragile insulin receptors become less sensitive (insulin resistant), which means that the pancreas must secrete even more insulin to keep clearing the blood of glucose. In later stages of the disease, the pancreas becomes "burned out" and can no longer produce adequate insulin. Insulin levels drop far below normal, allowing blood glucose to rise even higher and inflict greater damage.

Unfortunately, many early-stage diabetics are prescribed drugs (such as sulfonylureas) that are designed to boost insulin levels. Considering that insulin levels are already high, this strategy is counterproductive and may actually serve to hasten the disease by further exhausting the insulin receptors on cell membranes. Also, insulin itself is a powerful hormone that, in high levels, can inflict damage. Evidence suggests that high levels of insulin may suppress growth hormone synthesis and release among obese and overweight people (who are prone to hyperinsulinemia) (Luque RM et al 2006). There is also evidence that increased levels of insulin contribute to the proliferation of colorectal cells, which suggests that high levels of insulin may be a factor in the development of colorectal cancer (Tran TT et al 2006).

## **A PROGRAM FOR EARLY DIABETICS**

There are acute differences between the early stages of diabetes and the advanced stages. Thus, it doesn't make sense to treat all people with type 2 diabetes the same. In the early stages of the disease, people suffer from both hyperglycemia and hyperinsulinemia. Rather than take drugs that further increase the level of insulin in the blood, people with type 2 diabetes would do better to pursue therapies that increase the sensitivity of insulin receptors on the cell membranes.

One of the best defenses against mild to moderate type 2 diabetes and hyperinsulinemia is improved diet and exercise. Although the disease has a genetic component, many studies have shown that diet and exercise can prevent it (Diabetes Prevention Program Research Group 2002; Diabetes Prevention Program Research Group 2003; Muniyappa R et al 2003; Diabetes Prevention Program Research Group 2000). One study also showed that while some medications delay the development of diabetes, diet and exercise work better. Just 30 minutes a day of moderate physical activity, coupled with a 5 to 10 percent reduction in body weight, produces a 58 percent reduction in the incidence of diabetes among people at risk (Sheard NF 2003). The American Diabetes Association recommends a diet high in fiber and unrefined carbohydrates and low in saturated fat (Sheard NF et al 2004). Foods with a low glycemic index are especially recommended because they blunt the insulin response. For more information on glycemic index, see the chapter titled Obesity.

The high-carbohydrate, high-plant-fiber (HCF) diet popularized by James Anderson, MD, has substantial support and validation in the scientific literature as the diet of choice in the treatment of diabetes (Anderson JW et al 2004; Hodge AM et al 2004). The HCF diet is high in cereal grains, legumes, and root vegetables and restricts simple sugar and fat intake. The caloric intake consists of 50 to 55 percent complex carbohydrates, 12 to 16 percent protein, and less than 30 percent fat, mostly unsaturated. The total fiber content is between 25 and 50 g daily. The HCF diet produces many positive metabolic effects, including the following: lowered postmeal hyperglycemia and delayed hypoglycemia; increased tissue sensitivity to insulin; reduced low-density lipoprotein (LDL) cholesterol and triglyceride levels and increased high-density lipoprotein (HDL) cholesterol levels; and progressive weight loss.

A healthy diet for diabetics is also rich in potassium. Potassium improves insulin sensitivity, responsiveness, and secretion. A high potassium intake also reduces the risk of heart disease, atherosclerosis, and cancer. Insulin administration induces potassium loss (Khaw KT et al 1984; Norbiato G et al 1984).

People who are obese have a far greater tendency to develop type 2 diabetes than those who are relatively slim. Therefore, weight loss accompanied by increase in exercise and a healthy diet is effective for diabetes prevention and treatment (Mensink M et al 2003; Sato Y 2000; Sato Y et al 2003).

### **METFORMIN: INCREASING INSULIN SENSITIVITY**

In addition to diet and exercise, the prescription drug Metformin has been proven to increase insulin sensitivity in people with mild to moderate hyperglycemia. Metformin is now the most commonly prescribed oral antidiabetic drug in the world. It works by increasing insulin sensitivity in the liver (Joshi SR 2005). It also has a number of other beneficial effects, including weight loss, reduced cholesterol-triglyceride levels, and improved endothelial function.

Metformin is tolerated better than many other antidiabetic prescription drugs, but people with congestive heart failure or kidney or liver disease are not candidates for metformin therapy. Neither are people who use alcohol to excess. A benchmark assessment of kidney function, followed by an annual renal evaluation, is essential. Vitamin B12 levels should also be checked regularly because chronic use of metformin could cause a deficiency in both folic acid and vitamin B12, resulting in neurological impairment and disruption in homocysteine clearance. Also, metformin should not be used for two days before or after having an x-ray procedure with an injectable contrast agent because of the rare risk of lactic acidosis.

Metformin is effective on its own, but it may also be prescribed in combination with another class of insulin sensitizers called thiazolidinediones (TZDs; e.g., pioglitazone, or Actos®, and rosiglitazone, or Avandia®). TZDs increase insulin sensitivity and stimulate release of insulin from beta cells in the pancreas. TZD treatment also improves blood pressure and relieves vascular and lipid defects (Meriden T 2004). However, TZDs have potentially serious side effects, including liver toxicity, which requires regular monitoring of liver function (Isley WL 2003; Marcy TR et al 2004).

In addition to these two prescription drugs, many nutrients have been shown to increase insulin sensitivity, protect vulnerable cell membranes, and reduce the damaging effects of elevated glucose (see "Nutritional Supplementation for Diabetics," below). Ideally, a combination of improved diet, exercise, supplementation, and insulin-sensitizing prescription drugs can reverse mild to moderate hyperglycemia before stronger drugs are needed and permanent damage is done.

### **DRUG THERAPY FOR ADVANCED DIABETICS**

Some people, however, will not have the benefit of this knowledge before their type 2 diabetes advances to a more dangerous stage. In severe hyperglycemia, the pancreas becomes burned out after producing high levels of insulin for a long time. Insulin levels drop as a result of decreased production, and blood glucose levels are allowed to rise to very high, toxic levels. Although diet and exercise, along with supplementation, are still strongly recommended, a number of prescription drugs might also be necessary.

Sulfonylurea drugs stimulate pancreatic secretion of insulin. Unfortunately, they are often prescribed as first-line treatment for mild to moderate type 2 diabetics, even when their use is inappropriate. By increasing levels of insulin, which are already raised, sulfonylurea drugs actually hasten the progression of early type 2 diabetes by exhausting insulin receptors faster, which causes the pancreas to burn out more quickly. Sulfonylurea drugs should really be considered a “last resort” for people with severe hyperglycemia.

Insulin replacement therapy is also a last resort for type 2 diabetics. While insulin therapy is universal—and essential—among type 1 diabetics, it is reserved for only severe, refractory (nonresponsive to treatment) type 2 diabetics. Proper dosing and monitoring of blood glucose are essential as too much insulin causes low blood sugar and coma, and too little insulin creates hyperglycemia. A new delivery system for insulin was recently approved by the US Food and Drug Administration. This new system allows for inhaled insulin.

### ***What You Have Learned So Far***

- Diabetes is caused by abnormal metabolism of glucose, either because the body does not produce enough insulin or because the cells become desensitized to the effects of insulin.
- Type 1 diabetes is caused by an autoimmune reaction that destroys the insulin-producing beta cells in the pancreas. Type 2 diabetes is caused by decreased insulin sensitivity.
- Type 2 diabetes has reached epidemic proportions in America. The incidence of this disease, which is caused by obesity and genetic predisposition, has increased dramatically over the past five years. It is more common among older people than in other segments of the population, although it is also affecting children at increasing rates.
- People with mild to moderate type 2 diabetes should avoid drugs and therapies that increase levels of insulin. Their disease is characterized by elevated levels of both insulin and glucose. Instead, therapy should focus on strategies to increase insulin sensitivity.
- Possible complications in diabetes arise from damage to enzymes and other proteins that impair their function and from resulting damage to blood vessels. The subsequent decreased blood flow, increased vulnerability to oxidant stress, and decreased antioxidant capacity all interact to produce end-organ damage to the eyes, nerve tissue, kidneys, and cardiovascular system.
- Type 1 diabetics always need to use insulin therapy to replace their lost insulin.

## NUTRITIONAL SUPPLEMENTATION FOR DIABETICS

Type 1 diabetics will need to be on insulin therapy for life, although the supplements mentioned in this section may help offset some of the complications caused by diabetes (e.g., reduced antioxidant capacity and glycation) as well enhance glucose metabolism. Type 2 diabetics can counteract the progression of their disease by improving insulin sensitivity, enhancing glucose metabolism, and attempting to mitigate the complications of diabetes. The following supplements have been shown to improve blood sugar control or limit diabetic damage:

**Lipoic acid.** As a powerful antioxidant, lipoic acid positively affects important aspects of diabetes, including blood sugar control and the development of long-term complications such as disease of the heart, kidneys, and small blood vessels (Jacob S et al 1995, 1999; Kawabata T et al 1994; Melhem MF et al 2002; Nagamatsu M et al 1995; Song KH et al 2005; Suzuki YJ et al 1992).

Lipoic acid plays a role in preventing diabetes by reducing fat accumulation. In animal studies, lipoic acid reduced body weight, protected pancreatic beta cells from destruction, and reduced triglyceride accumulation in skeletal muscle and pancreatic islets (Doggrell SA 2004; Song KH et al 2005).

Lipoic acid has been approved for the prevention and treatment of diabetic neuropathy in Germany for nearly 30 years. Intravenous and oral lipoic acid reduces symptoms of diabetic peripheral neuropathy (Ametov AS et al 2003). Animal studies have suggested that lipoic acid is more effective when taken with gamma-linolenic acid (GLA) (Cameron NE et al 1998; Hounsom L et al 1998).

Diabetes also damages deep nerves that control vital organs, such as the heart and digestive tract. In a large clinical trial, people with diabetes who had symptoms caused by nerve damage affecting the heart showed significant improvement without significant side effects from 800 mg oral lipoic acid daily (Ziegler D et al 1997a,b).

**Biotin.** Biotin enhances insulin sensitivity and increases the activity of glucokinase, the enzyme responsible for the first step in the utilization of glucose by the liver. Glucokinase concentrations in diabetics are very low. Animal studies have shown that a high biotin diet can improve glucose tolerance and enhance insulin secretion (Zhang H et al 1996; Furukawa Y 1999).

**Carnitine.** An extensive body of literature supports the use of carnitine in diabetes (Mingrone G 2004). Carnitine lowers blood glucose and HbA1c levels, increases insulin sensitivity and glucose storage, and optimizes fat and carbohydrate metabolism. Carnitine deficiency is common in type 2 diabetes. In a large human trial, acetyl-L-carnitine helped prevent or slow cardiac autonomic neuropathy in people with diabetes (Turpeinen AK et al 2005).

**Carnosine.** Carnosine is a glycation inhibitor that has been shown to exhibit protective effects against diabetic nephropathy and reduce the formation of AGEs (Janssen B et al 2005; Yan H et al 2005).

**Chromium.** Chromium is an essential trace mineral that plays a significant role in sugar metabolism. Chromium supplementation helps control blood sugar levels in type 2 diabetes and improves metabolism of carbohydrates, proteins, and lipids. Several studies have shown encouraging results from chromium supplementation:

- A controlled human study of type 2 diabetics compared two forms of chromium (brewer's yeast and chromium chloride) (Bahijiri SM et al 2000). Both forms of chromium significantly improved blood sugar control. Positive results were also seen in two smaller human trials (Ghosh D et al 2002; Jovanovic L et al 1999).
- A large human trial compared the effects of 1000 mcg chromium, 200 mcg chromium, and placebo (Anderson RA et al 1997). HbA1c values improved significantly in the group receiving 1000 mcg after two months and in both chromium groups after four months. Fasting glucose was also lower in the group taking the higher dose of chromium.

**Coenzyme Q10.** Coenzyme Q10 (CoQ10) improves blood sugar control, lowers blood pressure, and prevents oxidative damage caused by disease. In a controlled human trial, type 2 diabetics given 100 mg CoQ10 twice daily experienced improved glycemic control as measured by lower HbA1c levels and blood pressure (Hodgson JM et al 2002). In a separate study, CoQ10 improved blood flow in type 2 diabetics, an outcome attributed to CoQ10's ability to lower vascular oxidative stress (Watts GF et al 2002). In a third study, improved blood flow correlated with decreased HbA1c (Playford DA et al 2003).

In animal studies, CoQ10 quenched free radicals, improved blood flow, lowered triglyceride levels, and raised HDL levels, suggesting a role for CoQ10 in preventing and managing complications of diabetes (Al-Thakafy HS et al 2004). Animal studies have also shown that CoQ10 levels are depleted by diabetes (Kucharska J et al 2000).

**Dehydroepiandrosterone.** Recent studies have yielded very encouraging results supporting dehydroepiandrosterone (DHEA) supplementation in diabetics. DHEA has been shown to improve insulin sensitivity and obesity in human and animal models

(Yamashita R et al 2005). Although mechanism of action is poorly understood, it is thought that DHEA improves glucose metabolism in the liver (Yamashita R et al 2005).

Animal studies have also demonstrated that DHEA increases beta cells on the pancreas, which are responsible for producing insulin (Medina MC et al 2006).

In humans, DHEA levels are sensitive to elevated glucose: higher glucose levels tend to be associated with decreased DHEA levels (Boudou P et al 2006). One proposed mechanism of action in humans is linked to DHEA's metabolism into testosterone. DHEA is an adrenal hormone that can be converted into either testosterone or estrogen. Studies have shown that testosterone improves insulin sensitivity in men, suggesting that DHEA's conversion into testosterone may be responsible for its beneficial effects in improving insulin sensitivity (Kapoor D et al 2005).

**Essential fatty acids.** In human experiments, omega-3 fatty acids lowered blood pressure and triglyceride levels, thereby relieving many of the complications associated with diabetes. In animals, omega-3 fatty acids cause less weight gain than other fats do; they have also been shown to have a neutral effect on LDL, while raising HDL and lowering triglycerides (Petersen M et al 2002). There are two types of essential fatty acids:

- **Omega-3.** Marine oil contains omega-3 fatty acids. The research on omega-3 fatty acids stems from studies of the Inuit (Eskimo) people, who seldom suffer from heart attacks even though their diets contain an enormous amount of fat from fish, seals, and whales, presumably because those sources of fat are very high in omega-3 fatty acids. Omega-3 fatty acids found in marine oil, lower blood triglyceride levels, contribute to "thinning" the blood, and also decrease inflammation (Ebbesson SO et al 2005). These effects partially explain many of fish oil's benefits.
- **Omega-6.** Diabetic neuropathy is a gradual degeneration of peripheral nerve tissue. There is some evidence that GLA, an omega-6 fatty acid, can be helpful if given long enough to work. In one double-blind, placebo-controlled study, 111 people with mild diabetic neuropathy received either 480 mg daily of GLA or placebo. After 12 months, the group taking GLA was doing significantly better than the placebo group in 13 out of 16 measures of nerve function, with patients whose diabetes was under control doing best (Keen H et al 1993). There is also evidence that GLA is more effective for diabetic neuropathy when it is combined with lipoic acid (Hounsom L et al 1998).

**Fiber.** It is difficult to overstate the benefits from fiber in regard to blood glucose control. Eating a diet rich in high-fiber foods prevents and reduces the harm caused by chronically elevated blood glucose.

One study reported the results of diabetic individuals consuming a diet supplying 25 g soluble fiber and 25 g insoluble fiber (about double the amount currently recommended by the American Diabetes Association). The fiber was derived from foodstuffs, with no emphasis placed on special or unusual fiber-fortified foods or fiber supplements. A high-fiber diet reduced blood glucose levels by an average of 10 percent (Chandalia et al 2000).

Fiber is also valuable because it produces a feeling of satiety, reducing the desire to overeat. Because high-fiber foods are digested more slowly than other foods, hunger pangs are forestalled. For the most part, fibrous foods are healthful (nutrient dense and low in fat).

Fiber should be added slowly, gradually replacing low-fiber foods, for the following reasons: (1) insulin and prescription drugs may have to be adjusted to accommodate lower blood glucose levels, and (2) without a gradual introduction of the new material, intestinal distress could occur, including bloating, flatulence, and cramps.

Some individuals prefer to bolster fiber volume by adding supplemental fiber in the form of pectin, gums, and mucilages to each meal. Calculate the amount of fiber gained from foodstuffs and supplement with enough to compensate for shortfalls. Monitor blood glucose levels closely to assess gains and to adjust oral or injectable hypoglycemic agents.

**Flavonoids.** Flavonoids are antioxidants that help reduce damage associated with diabetes. In animal studies, quercetin, a potent flavonoid, decreases levels of blood glucose and oxidants. Quercetin also normalizes levels of the antioxidants superoxide dismutase, vitamin C, and vitamin E. Quercetin is more effective at lower doses and ameliorates the diabetes-induced changes in oxidative stress (Mahesh T et al 2004).

**Magnesium.** People with diabetes are often deficient in magnesium, which is depleted both by medications and by the disease process (Eibl NL et al 1995; Elamin A et al 1990; Tosiello L 1996). One double-blind study suggested that magnesium supplementation enhanced blood sugar control (Rodriguez-Moran M et al 2003).

**N-acetylcysteine.** N-acetylcysteine (NAC) is a powerful antioxidant that is used to treat acetaminophen overdose. Among diabetic rats, it has also demonstrated the ability to protect the heart against endothelial damage and oxidative stress that is associated with heart attacks among diabetics. In one study, NAC was able to increase the availability of nitric oxide in diabetic rats, thus

improving their blood pressure as well as reducing the level of oxidative stress in their hearts (Xia Z et al 2006). In a human study examining the effects of broad-based antioxidants, NAC, in addition to vitamin C and vitamin E, was able to reduce oxidative stress after a moderate-fat meal (Neri S et al 2005).

**Silymarin.** In animal studies, silymarin was shown to improve insulin levels among induced cases of diabetes (Soto C et al 2004). A small, controlled clinical study evaluated type 2 diabetics with alcohol-induced liver failure (Velussi M et al 1997). Those receiving 600 mg silymarin daily experienced a significant reduction in fasting blood and urine glucose levels. Fasting glucose levels rose slightly during the first month of supplementation but declined thereafter from an average of 190 mg/dL to 174 mg/dL. As daily glucose levels dropped (from an average of 202 mg/dL to 172 mg/dL), HbA1c also substantially decreased. Throughout the course of treatment, fasting insulin levels declined by almost one-half, and daily insulin requirements decreased by about 24 percent. Liver function improved. A lack of hypoglycemic episodes suggests silymarin not only lowered blood glucose levels but also stabilized them.

**Vitamin B3.** Vitamin B3 (niacin) is required for the proper function of more than 50 enzymes. Without it, the body is not able to release energy or make fats from carbohydrates. Vitamin B3 is also used to make sex hormones and other important chemical signal molecules.

In the past, the use of niacin was discouraged in diabetic individuals because it was found to increase insulin resistance and degrade glycemic control, particularly at high doses (Sancetta SM et al 1951). However, emerging clinical evidence shows that niacin is both safe and effective for diabetics (Meyers CD et al 2004).

There is evidence that niacin reduces the risk of developing type 1 diabetes (Pocoit F et al 1993; Pozzilli P et al 1993). Niacinamide helps restore beta cells, or at least slow their destruction. Because niacin can disrupt blood sugar control in diabetics, individuals taking any form of niacin, including inositol hexaniacinate, must closely monitor blood sugar levels and discontinue treatment in the event of worsening of diabetic control. Inositol hexaniacinate has long been used in Europe to lower cholesterol levels and also to improve blood flow in individuals with intermittent claudication.

**Vitamin C.** Several preclinical studies evaluated vitamin C's role during mild oxidative stress. The aqueous humor of the eye provides surrounding tissues with a source of vitamin C. Since animal studies have shown that glucose inhibits vitamin C uptake, this protective mechanism may be impaired in diabetes (Corti A et al 2004). Supplementation with antioxidant vitamins C and E plays an important role in improving eye health (Peponis V et al 2004). High vitamin C intake depresses glycation, which has important implications for slowing diabetes progression and aging (Krone CA et al 2004).

Vitamin C, through its relationship to sorbitol, also helps prevent ocular complications in diabetes. Sorbitol, a sugar-like substance that tends to accumulate in the cells of people with diabetes, tends to reduce the antioxidant capacity of the eye, with a number of possible complications. Vitamin C appears to help reduce sorbitol buildup (Will JC et al 1996).

Vitamin C also has a role in reducing the risk of other diabetic complications. In one clinical study, vitamin C significantly increased blood flow and decreased inflammation in patients with both diabetes and coronary artery disease (Antoniades C et al 2004). Three studies suggest that vitamin C, along with a combination of vitamins and minerals (Farvid MS et al 2004), reduces blood pressure in people with diabetes (Mullan BA et al 2002) and increases blood vessel elasticity and blood flow (Mullan BA et al 2004).

**Vitamin E.** Vitamin E has been shown to significantly reduce the risk of developing type 2 diabetes (Montonen J et al 2004). One double-blind trial found a reduction in the risk of cardiac autonomic neuropathy, or damage to the nerves that supply the heart, which is a complication of diabetes (Manzella D et al 2001). Additional evidence documented benefits for diabetic peripheral neuropathy (Tutuncu NB et al 1998), blood sugar control (Kahler W et al 1993; Paolisso G et al 1993a,b, Paolisso G et al 1994), and cataract prevention (Paolisso G et al 1993a,b; Paolisso G et al 1994; Seddon JM et al 1994). In addition, vitamin E enhances sensitivity to insulin in type 2 diabetics (Paolisso G et al 1993a,b).

## **BOTANICAL SUPPLEMENTS FOR DIABETES**

Before insulin, botanical medicines were used to treat diabetes. They are remarkably safe and effective. However, because many botanical medicines function similarly to insulin, people taking oral diabetes medications or insulin should use caution to avoid hypoglycemia. Botanical medicines should be integrated into a regimen of adequate exercise, healthy eating, nutritional supplements, and medical support.

**Cinnamon.** Cinnamon has been used for several thousand years in traditional Ayurvedic and Greco-European medical systems. Native to tropical southern India and Sri Lanka, the bark of this evergreen tree is used to manage conditions such as nausea, bloating, flatulence, and anorexia. It is also one of the world's most common spices, used to flavor everything from oatmeal and apple cider to cappuccino. Recent research has revealed that regular use of cinnamon can also promote healthy glucose metabolism.

A study at the US Department of Agriculture's Beltsville Human Nutrition Research Center isolated insulin-enhancing complexes in cinnamon that are involved in preventing or alleviating glucose intolerance and diabetes (Anderson RA et al 2004). Three water-soluble polyphenol polymers were found to have beneficial biological activity, increasing insulin-dependent glucose metabolism by roughly 20-fold in vitro (Anderson RA 2004). The nutrients displayed significant antioxidant activity as well, as did other phytochemicals found in cinnamon, such as epicatechin, phenol, and tannin. Moreover, scientists at Iowa State University determined that these polyphenol polymers are able to upregulate the expression of genes involved in activating the cell membrane's insulin receptors, thus increasing glucose uptake and lowering blood glucose levels (Imparl-Radosevich J et al 1998).

**Coffee berry.** Coffee berry contains some well-studied phytochemicals such as chlorogenic acid, caffeic acid, ferulic acid, and quinic acid (Charles-Bernard M et al 2005). Some of coffee berry's most impressive effects can be seen in blood glucose management. Chlorogenic acid and caffeic acid are the two primary nutrients in coffee that benefit individuals with high blood sugar. Glucose-6-phosphatase is an enzyme crucial to the regulation of blood sugar. Since glucose generation from glycogen stored in the liver is often overactive in people with high blood sugar (Basu R et al 2005), reducing the activity of the glucose-6-phosphatase enzyme leads to reduced blood sugar levels, with consequent clinical improvements.

Chlorogenic acid has been shown to inhibit the glucose-6-phosphatase enzyme in a dose-dependent manner, resulting in reduced glucose production (Hemmerle H et al 1997). In a trial at the Moscow Modern Medical Center, 75 healthy volunteers were given either 90 mg chlorogenic acid daily or a placebo. Blood glucose levels of the chlorogenic acid group were 15 percent to 20 percent lower than those of the placebo group (Abidoff MT 1999). Chlorogenic acid also has an antagonistic effect on glucose transport, decreasing the intestinal absorption rate of glucose (Johnston KL et al 2003), which may help reduce blood insulin levels and minimize fat storage.

Caffeic acid has benefits for elevated blood sugar as well. At National Cheng Kung University in Taiwan, scientists determined that this acid increases glucose uptake into cells, helping remove it from the bloodstream (Cheng JT et al 2000). When researchers at nearby Taipei Medical College injected caffeic acid into diabetic rats, they saw a dose-dependent reduction in plasma glucose (Hsu FL et al 2000). However, a similar effect was not observed in normal rats, suggesting that insulin is not involved in this action. In a related experiment, the researchers observed that caffeic acid reduced elevated plasma glucose in insulin-resistant rats receiving a glucose challenge test (Hsu FL et al 2000).

**Garlic.** Allium is the active component in garlic and onions. Allium compounds are sulfur-donating compounds that help reconstitute glutathione, a major internal antioxidant. This mechanism is probably responsible for allium's positive effects. Allium has a number of positive effects that may help reduce the risk of diabetic complications, including the following:

- Reducing the risk of cardiovascular disease, including atherosclerosis (Breithaupt-Grogler K et al 1997; Efendy JL et al 1997; Koscielny J et al 1999; Turner B et al 2004)
- Decreasing oxidative stress (Dhawan V et al 2004)
- Promoting weight loss and insulin sensitivity in animal models of diabetes (Elkayam A et al 2003)
- Lowering blood pressure (Auer W et al 1990; Sharifi AM et al 2003; Silagy CA et al 1994; Wilburn AJ et al 2004)
- Improving cholesterol profile (Durak I et al 2004; Gardner CD et al 2001; Holzgartner H et al 1992; Isaacsohn JL et al 1998; Kannar D et al 2001; Kris-Etherton PM et al 2002; Mader FH 1990; Neil HA et al 1996; Silagy CA et al 1994; Steiner M et al 1996; Superko HR et al 2000; Warshafsky S et al 1993)

**Green tea.** The compounds in these plants, including epicatechin, catechin, gallic acid, and epigallocatechin, are powerful antioxidants, particularly against pancreas and liver toxins (Okuda T et al 1983). Animal studies have shown that epigallocatechins, in particular, may have a role in preventing diabetes (Crespy V et al 2004). In studies with rats, epigallocatechins prevented cytokine-induced beta cell destruction by downregulating inducible nitric oxide synthase, which is a pro-oxidant (Kim MJ et al 2004; Song EK et al 2003). This process could help slow the progression of type 1 diabetes. In vitro studies have also shown that green tea suppresses diet-induced obesity (Murase T et al 2002), a key risk factor in developing diabetes and metabolic syndrome (Hung PF et al 2005).

**Ginkgo biloba.** Animal studies demonstrate that ginkgo improves glucose metabolism in muscle fibers and prevents atrophy (Punkt K et al 1999). Animal studies also show that Ginkgo biloba extracts significantly inhibit postmeal sugar levels and act as antihyperglycemic agents (Tanaka S et al 2004).

Ginkgo biloba extract has been shown to prevent diabetic retinopathy in diabetic rats, suggesting it has a protective effect in human diabetics (Doly M et al 1988). In a preliminary clinical trial (Huang SY et al 2004), type 2 diabetics were given ginkgo extract orally for three months, which significantly reduced free radical levels, decreased fibrinogen levels, and improved blood viscosity. Ginkgo extracts also improved retinal capillary blood flow rate in type 2 diabetic patients with retinopathy.

Ginkgo has also been observed to lower blood glucose levels. It was studied in type 2 diabetics at a dose of 120 mg for three months. Ginkgo supplementation produced an increase in liver metabolism of insulin and oral hypoglycemic medications, which corresponded to a reduction in plasma glucose levels (Kudolo GB 2001). Type 2 diabetics with pancreatic exhaustion received the

most benefit. Ginkgo does not appear to increase beta cell production; rather it enhances liver uptake of existing insulin, thereby reducing high insulin levels.

**Vaccinium myrtillus (bilberry).** Studies of diabetic rats show that bilberry decreases vascular permeability (Cohen-Boulakia F et al 2000). Studies of diabetic mice receiving an herbal extract containing bilberry demonstrated significantly decreased blood glucose levels (Petlevski R et al 2001; Petlevski R et al 2003).

A double-blind, placebo-controlled trial of bilberry extract in 14 people with diabetic retinopathy or hypertensive retinopathy (damage to the retina caused by diabetes or hypertension, respectively) found significant improvements in the treated group (Bone K 1997). Other open clinical trials in humans also showed benefits. A preliminary study of 31 people with retinopathy documented that bilberry reduced vascular permeability and reduced hemorrhage (Scharer A et al 1981).

## LIFE EXTENSION FOUNDATION RECOMMENDATIONS

Diabetes prevention or living with diabetes begins with exercise, weight loss if necessary, and dietary modifications. A high-fiber, plant-based diet has been shown to improve type 2 diabetes and to encourage weight loss.

Under no circumstances should people suddenly stop taking diabetic drugs, especially insulin. A type 1 diabetic will never be able to stop taking insulin. However, it is possible to improve glucose metabolism, control, and tolerance with the following supplements:

- **R-lipoic acid**—210 to 420 milligrams (mg) daily
- **L-carnitine**—500 to 1000 mg twice daily
- **Carnosine**—500 mg twice daily
- **Chromium** (preferably polynicotinate)—500 to 1000 mcg daily
- **CoQ10**—100 to 300 mg daily
- **DHEA**—15 to 75 mg early in the day, followed by blood testing after three to six weeks to ensure optimal levels
- **EPA/DHA**—1400 mg EPA and 1000 mg DHA daily
- **Fiber** (guar, pectin, or oat bran)—20 to 30 grams (g) daily at least, up to 50 g daily
- **GLA**—900 to 1800 mg daily
- **Quercetin**—500 mg daily (water-soluble form)
- **Magnesium** (preferably magnesium citrate)—160 mg up to three times daily
- **NAC**—500 to 1000 mg daily
- **Silymarin**—containing 900 mg Silybum marianum standardized to 80 percent Silymarin, 30 percent Silibinin, and 4.5 percent Isosilybin B
- **Vitamin C**—at least 2000 mg daily
- **Vitamin E**—400 international units (IU) daily (with 200 mg gamma tocopherol)
- **Garlic**—1200 mg daily
- **Green tea extract:** 725 mg green tea extract (minimum 93 percent polyphenols)
- **Ginkgo biloba**—120 mg daily
- **Bilberry extract**—100 mg daily
- **B complex**—Containing the entire B family, including biotin and niacin
- **Cinnamon extract**—125 mg (Cinnamomum cassia) standardized to 0.95 percent trimeric and tetrameric A-type polymers (1.2 mg) three times daily
- **Coffee berry extract**—100 mg (Coffee arabica) extract (whole fruit) standardized to 50 percent total phenolic acids (50 mg) and 15,000 Micromoles per gram ( $\mu\text{mole/g}$ ) ORAC- three times daily

## DIABETES SAFETY CAVEATS

An aggressive program of dietary supplementation should not be launched without the supervision of a qualified physician. Several of the nutrients suggested in this protocol may have adverse effects. These include:

### Bilberry

- Consult your doctor before taking Bilberry if you take warfarin (Coumadin). Bilberry has blood-thinning properties.
- Bilberry can cause gastrointestinal symptoms such as nausea and diarrhea.

### Chromium

- Consult your doctor before taking chromium if you have hyperglycemia or type 2 diabetes. See your doctor and monitor your

blood glucose level frequently if you take chromium and have hyperglycemia or type 2 diabetes.

## **Cinnulin**

- Cinnulin can lower plasma glucose levels.
- Consult your doctor before taking cinnulin if you have hyperglycemia or type 2 diabetes. See your doctor and monitor your blood glucose level frequently if you take cinnulin and have hyperglycemia or type 2 diabetes.

## **Coenzyme Q10**

- See your doctor and monitor your blood glucose level frequently if you take CoQ10 and have diabetes. Several clinical reports suggest that taking CoQ10 may improve glycemic control and the function of beta cells in people who have type 2 diabetes.
- Statin drugs (such as lovastatin, simvastatin, and pravastatin) are known to decrease CoQ10 levels.

## **Coffee Berry**

- Coffee berry can lower plasma glucose levels.
- Consult your doctor before taking coffee berry if you have hyperglycemia or type 2 diabetes. See your doctor and monitor your blood glucose level frequently if you take coffee berry and have hyperglycemia or type 2 diabetes.

## **DHEA**

- Do not take DHEA if you could be pregnant, are breastfeeding, or could have prostate, breast, uterine, or ovarian cancer.
- DHEA can cause androgenic effects in woman such as acne, deepening of the voice, facial hair growth and hair loss.

## **EPA/DHA**

- Consult your doctor before taking EPA/DHA if you take warfarin (Coumadin). Taking EPA/DHA with warfarin may increase the risk of bleeding.
- Discontinue using EPA/DHA 2 weeks before any surgical procedure.

## **Fiber**

- Take fiber supplements with a full 8-ounce glass of water.
- Drink eight 8-ounce glasses of water daily while taking fiber.

## **Folic acid**

- Consult your doctor before taking folic acid if you have a vitamin B12 deficiency.
- Daily doses of more than 1 milligram of folic acid can precipitate or exacerbate the neurological damage caused by a vitamin B12 deficiency.

## **GLA**

- Consult your doctor before taking GLA if you take warfarin (Coumadin). Taking GLA with warfarin may increase the risk of bleeding.
- Discontinue using GLA 2 weeks before any surgical procedure.
- GLA can cause gastrointestinal symptoms such as nausea and diarrhea.

## **Garlic**

- Garlic has blood-thinning, anticlotting properties.
- Discontinue using garlic before any surgical procedure.
- Garlic can cause headache, muscle pain, fatigue, vertigo, watery eyes, asthma, and gastrointestinal symptoms such as nausea and diarrhea.
- Ingesting large amounts of garlic can cause bad breath and body odor.

## **Ginkgo Biloba**

- Individuals with a known risk factor for intracranial hemorrhage, systematic arterial hypertension, diabetes, or seizures should avoid ginkgo.
- Do not use prior to or after surgery.
- Avoid concomitant use of ginkgo with NSAIDS, blood thinners, diuretics, or SSRI's.
- Gastrointestinal symptoms (nausea and diarrhea) may occur.
- Allergic skin reactions may occur.
- Elevations in blood pressure may occur.

## **Green Tea**

- Consult your doctor before taking green tea extract if you take aspirin or warfarin (Coumadin). Taking green tea extract and aspirin or warfarin can increase the risk of bleeding.
- Discontinue using green tea extract 2 weeks before any surgical procedure. Green tea extract may decrease platelet aggregation.
- Green tea extract contains caffeine, which may produce a variety of symptoms including restlessness, nausea, headache, muscle tension, sleep disturbances, and rapid heartbeat.

## **L-Carnitine**

- L-carnitine can cause gastrointestinal symptoms such as nausea and diarrhea.

## **Lipoic Acid**

- Consult your doctor before taking lipoic acid if you have diabetes and glucose intolerance. Monitor your blood glucose level frequently. Lipoic acid may lower blood glucose levels.

## **Magnesium**

- Do not take magnesium if you have kidney failure or myasthenia gravis.

## **NAC**

- NAC clearance is reduced in people who have chronic liver disease.
- Do not take NAC if you have a history of kidney stones (particularly cystine stones).
- NAC can produce a false-positive result in the nitroprusside test for ketone bodies used to detect diabetes.
- Consult your doctor before taking NAC if you have a history of peptic ulcer disease. Mucolytic agents may disrupt the gastric mucosal barrier.
- NAC can cause headache (especially when used along with nitrates) and gastrointestinal symptoms such as nausea and diarrhea.

## **Niacin (nicotinic acid)**

- Do not take high doses of nicotinic acid (1.5 to 5 grams daily or more) if you have liver dysfunction, an unexplained elevation in your serum aminotransferase (transaminase) level, active peptic ulcer disease, arterial bleeding, or if you consume large amounts of alcohol.
- Consult your doctor before taking high doses of nicotinic acid if you have a history of jaundice, peptic ulcer disease, gastritis, disease of the liver or bile ducts, gout, kidney dysfunction, or cardiovascular disease (especially acute myocardial infarction or unstable angina).
- Consult your doctor before taking high doses of nicotinic acid if you have diabetes. High doses of nicotinic acid can negatively affect glucose tolerance. Monitor your serum glucose level frequently if you take nicotinic acid and have diabetes.
- Have your doctor monitor your serum aminotransferase level if you take high-doses of nicotinic acid.
- Nicotinic acid may cause flushing, principally of the face, neck, and chest. This flushing is thought to be prostaglandin-prostacyclin mediated. Histamine may also play a role in the flushing.
- Nicotinic acid can cause dizziness, palpitations, rapid heartbeat, shortness of breath, sweating, chills, insomnia, nausea, vomiting, abdominal pain, and muscle pain.
- High doses of nicotinic acid can cause blurred vision, macular edema, toxic amblyopia, and cystic maculopathy.

## Quercetin

- Quercetin can cause headache, mild tingling of the extremities, and gastrointestinal symptoms such as nausea.

## Vitamin B1 (Thiamin)

- Consult your doctor before taking vitamin B1 for a thiamin deficiency, lactic acidosis secondary to thiamin deficiency, Wernicke-Korsakoff syndrome, Wernicke's encephalopathy, or Korsakoff's psychosis.

## Vitamin B2 (riboflavin)

- High doses of vitamin B2 (riboflavin) may interfere with the Abbott TDx drugs-of-abuse assay.
- Riboflavin absorption is increased in hypothyroidism and decreased in hyperthyroidism.
- If you are taking nucleoside reverse-transcriptase inhibitors, even a mild riboflavin deficiency can increase your risk of lactic acidosis.

## Vitamin B6

- Do not take 5 milligrams or more of vitamin B6 daily if you are being treated with levodopa, unless you are taking carbidopa at the same time.

## Vitamin B12 (cyanocobalamin)

- Do not take cyanocobalamin if you have Leber's optic atrophy.

## Vitamin C

- Do not take vitamin C if you have a history of kidney stones or of kidney insufficiency (defined as having a serum creatine level greater than 2 milligrams per deciliter and/or a creatinine clearance less than 30 milliliters per minute).
- Consult your doctor before taking large amounts of vitamin C if you have hemochromatosis, thalassemia, sideroblastic anemia, sickle cell anemia, or erythrocyte glucose-6-phosphate dehydrogenase (G6PD) deficiency. You can experience iron overload if you have one of these conditions and use large amounts of vitamin C.

## Vitamin E

- Consult your doctor before taking vitamin E if you take warfarin (Coumadin).
- Consult your doctor before taking high doses of vitamin E if you have a vitamin K deficiency or a history of liver failure.
- Consult your doctor before taking vitamin E if you have a history of any bleeding disorder such as peptic ulcers, hemorrhagic stroke, or hemophilia.
- Discontinue using vitamin E 1 month before any surgical procedure.

For more information see the Safety Appendix

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