Prevention and Treatment of Diabetes with Natural Therapeutics

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Introduction

Diabetes Mellitus (DM) is a group of diseases, all of which are characterized by elevated blood sugar levels. In the United States it is estimated that over 20 million people have one form of diabetes or another1. There are many different forms of the disease, each caused by different factors. Some causes of diabetes are still unknown. Diabetes is concerning because high blood sugar causes damage to many parts of the body, including blood vessels, heart, eyes, kidneys and nerves. This damage can lead to kidney failure, requiring transplant or dialysis, heart attacks, heart failure and stroke.

There are a few key words and concepts helpful in understanding diabetes, the problems, or "complications" occurring with the disease and the potential benefits of various types of treatment. The section below "Definitions and Concepts" should help guide you through the remainder of this resource. We hope this report helps you to understand diabetes better, and helps outline some of the pros and cons of different treatments.

Definitions and Concepts

Definitions

Glucose: Glucose is the type of sugar used by the body for energy. Most types of food whether table sugar, fat or even meat is typically converted to glucose before it is used by the body for fuel.

Hyper/hypoglycemia: "Glycemia" means glucose in the blood, therefore "hyperglycemia" suggests sugar in the blood is too high, while "hypoglycemia" suggests blood sugar is too low. For most purposes, "hypoglycemia" is blood glucose lower than 70 (mg/dl) and "hyperglycemia" is blood glucose higher than 190 (mg/dL), however the definition of "hyperglycemia" really depends on the time of day in relation to a meal.

Insulin: Insulin is a hormone released by beta cells of the pancreas in response to the intake of sugar or other carbohydrates. It attaches to the outside of cells in the body, resulting in a signal allowing cells to take the sugar inside the cell to use as fuel.

Calories: Calories are the way energy is measured in food. For each piece of food you eat, a certain amount of that food is turned into useful energy for your body. This energy content is described in units called calories. If calorie intake exceeds calories use, calories are stored and weight gain results. If calories intake is less than calories used, then weight loss results. Foods vary in the number of calories they contain per serving. Fat has more calories than either carbohydrates or proteins per gram weight.

Carbohydrate: Carbohydrates are one of the three major types of foods. There are various types of carbohydrates, but the easiest way to think of carbohydrates is divide them into simple, complex and fiber. Simple carbohydrates include table sugar and fruit sugar (called fructose). Complex carbohydrate foods include starchy cereal grains like wheat, vegetables like yams and potatoes and beans. Fiber is not digestible, i.e. it is not used for fuel, but rather helps with the digestive process by slowing down the absorption of sugar from food.

Fat: Fat is another of the three major types of food. Examples of fat in food include cooking oils, butter and the fat on meat products. Fat is essential in nutrition, but is higher in calories than carbohydrates.

Protein: Protein is the third major type of food used by the body. Protein is used for energy, but it is also used for repair as well as for numerous reactions and processes within the body. Examples of high protein foods include meat, nuts, beans and whole grains. Insulin is available as drug treatment for diabetes when our own production is not enough.

Pancreas: The pancreas is a small organ in the abdomen that helps with digestion and absorption of food. The pancreas makes and secretes insulin in response to food. The pancreas also makes and secretes digestive enzymes to help break down food into smaller bits so it can be absorbed. The pancreas makes lots of chemical messengers, not all of which have known actions. Within the pancreas there are multiple types of cells. The "beta" cells are the cells that make insulin.

Liver: The liver is large organ on the right hand side of the body, under the rib cage. The liver helps process food after is eaten and it also stores glucose and fat to help keep blood sugar normal in times between meals. The liver also serves as a detoxification organ, filtering toxins and chemicals from our bodies.

Obesity: Obesity is a term used to describe body weight well above the ideal weight for a person's height. Body weight is described in a range between normal/ideal, progresses to overweight and then on to obese. "Overweight" and "obese" are defined by a measurement called a body mass index, or BMI. Your BMI is a ratio of weight and height. A normal, healthy body weight is considered a BMI between 20-25. A BMI of 25-30 is considered overweight, and a BMI greater than 30 is obesity.

Concepts

Cells, tissues and organs: Cells, tissues and organs are the basic building blocks of the human body. Cells join together to make tissues, and tissues in turn combine to make organs. A muscle cells combine to make myocardium, or heart tissue, which then combined with other tissues like arteries to make the heart organ.

Insulin resistance: Insulin resistance is a term used when the body does not respond to insulin the way it should. Insulin action requires binding a receptor, like a key entering a lock to open a door. When the lock, or receptor, gets sticky the lock no longer works properly. Insulin resistance occurs at many levels; it can be mild or severe and it can worsen over time. When insulin resistance occurs, sugar stays in the blood longer leading to higher levels in the blood.

Insulin deficiency: Insulin deficiency is present when the pancreas can no longer secrete enough insulin to lower blood sugar to normal levels. Insulin deficiency results when insulin resistance has been present for some time and the pancreas can no longer keep up with the demand. Insulin deficiency can also result from damage to the pancreas. For example, in Type 1 diabetes and in Latent Autoimmune Diabetes (see Types of Diabetes below), antibodies are produced against the pancreas causing destruction of the organ.

Metabolism: The term "metabolism" refers to the process by which food (and therefore calories) are broken down for energy production by the body. Like in different types of cars, fuel is burned by the different people at different rates. In humans, metabolic rate is affected by age, various hormones (including insulin), gender, genetics, health status and level of exercise. Exercise increases metabolic rate, i.e. more calories need to be burned to maintain body weight.

Genetics: Genetics refer to our inherited traits that we received from our parents. Genes control everything that gets made in the body, including the levels and actions of various hormones and enzymes for body processes. We have our genes forever (at least until "gene therapies" are perfected). Fortunately genes are also controlled by their environments, and therefore by changing our internal environment we can also change the function of our genes (this Concept is called epigenetics). An abnormal change in a gene is called a mutation.

Autoimmune: The term "autoimmune" refers to conditions in which the body produces antibodies against its own tissues. Antibodies are proteins the body makes to help the immune system latch on and attack foreign particles like bacteria and viruses. In autoimmune conditions, antibodies are formed against particles that are not foreign, like the cells in the pancreas.

Heart disease and atherosclerosis: Heart disease refers to a variety of conditions all affecting the heart. Heart disease is most classically hardening of the arteries, or atherosclerosis, of the arteries that supply blood to the heart itself. However congestive heart disease, or heart failure, is another type of heart disease in which the heart gets too floppy or too stiff and is unable to pump blood properly. Hardening of the arteries can occur in any artery in the body, including the arteries to the kidneys, brain and legs. A "heart attack" occurs when blood flow is limited to heart; this can occur because of spasms of the arteries, clots breaking lose and lodging in the arteries or because the arteries gradually get too narrow to allow blood

through.

Stroke: A stroke is similar to a heart attack, except it occurs in the brain and not in the heart. Strokes occur when blood flow to the brain is limited, which can occur because of spasm, clots or gradual narrowing. Strokes are actually more serious than heart attacks because the brain is more sensitive to limited blood flow and the brain cannot repair itself nearly as well as the heart.

Oxidation and Inflammation: A normal part of metabolism is to generate molecules known as free radicals. These molecules can lead to what is termed "oxidative damage" if they are present in very large amounts and if the body doesn't have enough antioxidants to neutralize them. Antioxidants are increased by the foods that we eat (as well as by avoiding certain foods!) and some are made by our bodies from protein. Free radicals are shown to be present at higher levels in people with DM than those without it. Studies indicate that this oxidative damage can lead to the blood vessel damage associated with DM7. Recent research has shown there really is a lot of overlap between oxidation and inflammation; these processes share common pathways.

Glycosylation: If there is too much glucose in the blood stream it can attach itself to proteins throughout the body via a process called glycosylation. Blood vessels, nerves and parts of the eye are particularly vulnerable because smaller vessels (microvessels, see below) supply blood to these tissues. Glycosylation is thought to contribute to both inflammatory and oxidative damage that occurs to the large and small blood vessels in the body.

Macro vs. microvascular: Vascular refers to vessels, or artery supplying blood to the tissues. "Macro" refers to larger vessels or arteries supplying blood to organs. "Micro" refers to small vessels supplying blood to tissues. In some cases, like in the kidney, both macro and microvascular structures exist. For example, the large renal artery is a "macrovessel" carrying blood to the entire kidney organ, but the kidney has smaller structures inside of it where the arteries get smaller becoming "microvessels".

Types of Diabetes Mellitus (DM)

Type I Diabetes Mellitus (T1DM) occurs as the result of an autoimmune disorder which damages the pancreas, ultimately leading to reduced or absent insulin secretion. T1DM usually begins in childhood, although not always, and accounts for 5-10% of those diagnosed with DM. The initial presentation of hyperglycemia can happen slowly or rapidly. However, the eventual outcome is complete, or near complete, loss of ability by the pancreas to secrete insulin necessitating prescription insulin.

Type II diabetes (T2DM) accounts for 90-95% of those diagnosed with DM. People with T2DM often exhibit high blood glucose and normal, slightly elevated, or slightly decreased insulin secretion. Unlike T1DM, T2DM is not an autoimmune condition, but rather is a disease with contributions from diet, stress and sedentary lifestyle. T2DM also often presents with insulin resistance. In insulin resistance, the pancreas is able to secrete insulin, but the cells don't respond to it efficiently; this process inhibits the cell from absorbing glucose, which in turn, keeps blood glucose levels high. Because T2DM is a progressive disease without changing the metabolic environment, many people do ultimately require insulin therapy.

T2DM is primarily seen in adults, however, there is an alarming trend of an increasing number of children and adolescents who are exhibiting impaired fasting glucose and insulin resistance as well. As with adults, this is often associated with obesity2.

The terminology "double diabetes" is used when insulin resistance (which, as mentioned, is usually seen with T2DM) is present with T1DM3. Double diabetes occurs in people with T1DM who have prolonged poor blood sugar control, or live a lifestyle consistent with developing T2DM.

Another type of DM is latent autoimmune diabetes in adults, or LADA. It is so named because it demonstrates some of the similar autoimmune characteristics of T1DM, however, it usually occurs in adults. Oral medications are have limited

usefulness in LADA as the primary dysfunction is reduced insulin production, therefore patients typically require insulin earlier to maintain normal blood sugar than in T2DM4.

Gestational Diabetes (GDM) occurs during pregnancy and usually resolves upon delivery. However, a mother who had GDM during pregnancy remains at a higher risk for developing T2DM than a mother who did not have GDM. Unfortunately, a child is also at an increased risk of developing T2DM, if their mother had GDM during pregnancy. GDM is reported in approximately 4% of pregnancies in the US1.

Some people demonstrate a decreased amount of insulin secretion, but it does not appear to be the result of an autoimmune disorder. This type of DM is referred to as Idiopathic Diabetes (IDM). People with IDM have varying degrees of need for extra insulin 1. Certain genetic mutations may be associated with IDM, but unfortunately routine clinical testing for these mutations is not available.

Complications of Diabetes Mellitus

Diabetes ketoacidosis (DKA) is an extremely serious possible complication of diabetes. DKA is most commonly seen in T1DM, and when severe, can lead to coma or even death. It often first presents, however, with symptoms such as increased urination, increased thirst, fatigue, nausea and/or vomiting.

People with T1DM have increased risk for other autoimmune diseases as well, including thyroid disease and celiac disease1. Celiac tissue is a condition in which your body produces antibodies to a protein in wheat and other grains (called gluten); these antibodies react with tissues in the intestines and cause pain and damage to the lining of the intestines. If you have Type 1 diabetes, your physician should test you to see if you also have thyroid or celiac disease.

Long standing elevations of blood glucose seen in DM can also lead to long term complications and/or failure of the eyes, kidneys, blood vessels, nerves and heart1. Complications of the retina of the eye, the kidneys and the nerves are referred to as retinopathy, nephropathy and neuropathy respectively.

The latest statistics regarding the prevalence of these complications are5:

- Heart disease and stroke account for about 65% of deaths in people with DM.
- Adults with DM have heart disease death rates about 2 to 4 times higher than adults without DM.
- The risk for stroke is 2 to 4 times higher and the risk of death from stroke is 2.8 times higher among people with DM.
- About 73% of adults with DM have high blood pressure.
- DM is the leading cause of blindness in adults 20-74 years of age.
- Mexican Americans are almost twice as likely and non-Hispanic blacks are almost 50% as likely to develop diabetic retinopathy as non-Hispanic whites.
- DM is the leading cause of kidney failure. In 2002, a total of 153,730 people with end stage renal disease due to diabetes were living on chronic dialysis or with a kidney transplant.
- Non-Hispanic blacks are 2.6 to 5.6 times as likely, Mexican Americans are 4.5 to 6.6 times more likely and American Indians are 6 times more likely to suffer from kidney disease from DM.
- About 60% to 70% of people with DM have mild to severe forms of nervous system damage. The results of such damage include impaired sensation or pain in the feet or hands, slowed digestion of food in the stomach, carpal tunnel syndrome, and other nerve problems.
- More than 60% of lower-limb amputations not related to trauma occur in people with DM.
- The rate of amputation for people with DM is 10 times higher than for people without DM.
- Mexican Americans are 1.8 times as likely, non-Hispanic Blacks are 2.7 times as likely, and American Indians are 3 to 4 times as

likely to suffer from amputation from DM.

- Men with DM are 2 times more likely to experience erectile dysfunction as men without DM
- Women with T1DM are twice as likely to experience sexual dysfunction than women without DM
- People with DM are more susceptible to many other illnesses and, often have worse prognoses, and are more likely to die from illnesses such as pneumonia or influenza than people who do not have DM

Mechanisms of Complications Associated with Diabetes Mellitus

No single mechanism can explain all of the damage than can occur in diabetes. One mechanism that seems to be very important in multiple complications is oxidative damage and inflammation (see Concepts). Another process that lead to diabetes related organ damage is the accumulation of sorbitol in certain tissues and organs. Sorbitol is manufactured in the body from glucose. When glucose levels are elevated, sorbitol is produced inside the cells faster than it can be broken down. Since sorbitol cannot cross cell membranes, it builds up inside the cells and draws water inside. This sorbitol-induced swelling is believed to be one of the main causes of tissue damage in people with diabetes.

Clinical Markers Used for Diabetes Monitoring

The following descriptions discuss some of the clinical markers that health care providers monitor in order to determine an individual's risk of such complications. Understanding what each of these markers means can help you ask for the right testing by your doctor, and can help you learn how things you do day to day, like exercise and diet, affect your risk for complications.

Blood glucose should be monitored by patient and provider alike. Home glucometers are easily used and should be prescribed for you by your doctor or diabetes educator. Self-glucose checking does require "pricking" your finger with a small needle, or lancet. Fortunately lancets have gotten slimmer and slimmer and now are virtually pain free.

"Continuous blood glucose monitoring" (CBGM) has become available recently and is extremely useful for people with T1DM. CBGM allows for near "real-time" measurement of blood sugar at all times of day, allowing a person to see changes happening in blood sugar and respond with changes in treatment or diet. CBGM requires a canula to be placed under the skin, where it is left in place for several days. Unfortunately CBGM still requires calibration with a glucometer and so self-sticks are not avoided (yet).

Hemoglobin A1C (HbA1c) is a measure of glycosylation of red blood cells (recall glycosylation is a process where glucose sticks to proteins in the body). HbA1c is monitored because it can give the doctor an idea of how well blood glucose has been controlled over the previous few months. Lowering HbA1c, signifying lowering of average blood sugar, is known to reduce risk for developing complications in diabetes, and reduced the risk of death from cardiovascular disease. HbA1c compares well to an average blood glucose and for this reason is being replaced as the principal measure of blood glucose control in monitoring diabetes. A1c-derived average glucose (AG) will be replacing hemoglobin A1c because patients are more likely to relate changes in their AG to their observations of their blood sugar monitoring. The hope is that by using AG, patients will be able to better adjust their diet and exercise plan. Since most home glucometers provide a 14 or 30-day average, patients can monitor their own average and related this to their AG measured in their doctor's office. The current recommendation for hemoglobin A1c is less than 7%; this corresponds to an AG of approximately 155 mg/dL.

DM can lead to dysfunction in blood lipid levels, including LDL ("bad") and HDL ("good") cholesterols as well as triglycerides. The link between dysfunctional lipid levels and cardiovascular disease, including atherosclerosis, is well known, so these levels will be monitored carefully as well. The recommended levels for LDL, HDL and triglycerides are less than 100 mg/dl (LDL), greater than 40 mg/dL for men and

greater than 50 mg/dL for women (HDL) and less than 150 mg/dL (triglycerides). Really HDL should be as high as possible; exercise is the best way to raise HDL cholesterol.

High-sensitivity or cardiac C-reactive protein (hsCRP) is an inflammatory marker which has been independently associated with cardiovascular disease. hsCRP is thought to represent degrees of vascular inflammation in the body. Clinical monitoring for hsCRP is controversial because of the lack of clinical trials that suggest lowering hsCRP impacts survival from heart disease.

Lastly blood pressure is monitored, because, like DM, increased blood pressure is associated with kidney disease and retinopathy (a disease of the eye). A blood pressure recommended for people with diabetes is less than 130/80 mmHg.

Although blood sugar control as well as optimal blood cholesterol and blood pressure are all important, epidemiologic studies have taught us that blood pressure and blood cholesterol reductions seem to have greater benefit for reducing risk for cardiovascular disease and death. All three elements of health should be optimized, however when choices have to be made, cholesterol lowering and blood pressure lowering appear more important for reducing risk of major heart disease and stroke9,10. Blood glucose control remains very important for the prevention of complications in small blood vessels.

Every year recommendations compiled creating a "standard of care" for treating patients with DM. As mentioned earlier, the management of DM includes daily blood glucose monitoring by the patient. The goal is to maintain levels as close as possible to the normal range, which for samples taken upon rising or before meals, should be 90-130 mg/dL. After eating, the blood glucose should not go above 180 mg/dL. Hemoglobin A1C is also monitored, and the goal is < 7%. Blood pressure should be ≤ 130/80 and blood lipids goals are: LDL ≤ 100 mg/dL, triglycerides ≤ 150 mg/dL and HDL ≥ 40 mg/dL for men and ≥ 50 mg/dL for women in patients with DM 6.

Lifestyle Changes in the Treatment of Diabetes

To help meet the goals discussed above a variety of treatment methods are employed. Lifestyle changes, including dietary and exercise, as well as quitting smoking, remain of paramount importance to good blood sugar, cholesterol and blood pressure control in diabetes. According to clinical trial results, lifestyle changes appear to be as or more effective than insulin therapy for people with poorly controlled diabetes. 11 Patients with DM are encouraged to have no more than 7% of their dietary calories come from fat, and to eliminate trans fats. Limiting carbohydrate intake to reduce blood glucose, and monitoring the glycemic index and/or glycemic load (see below) of carbohydrates are helpful as well6. Caloric restriction (eating less) is recommended if weight loss is necessary.

Exercise

Exercise recommendations include at least 150 minutes per week of moderate intensity aerobic activity reaching 50-70% of the maximum heart rate (or maximum effort) for the individual. In addition, or alternately, patients can do 90 minutes per week of vigorous aerobic activity reaching at least 70% of the maximum heart rate or maximum effort (maximum heart rate can be estimated by 220-your age). Also, for those patients for whom it is appropriate (determined by health care provider), resistance training with weights three times per week is also recommended. The eventual training goal should include 3 sets of 8-10 repetitions with emphasis on each major muscle group. The exercise sessions can be spread throughout the week, with the suggestion to have no more than 2 days in a row without some sort of physical activity6. While these are the general recommendations for people with DM, it is important to have the provider tailor individual suggestions based on the patient's glycemic control and presence of other complications.

Recommendations change with other populations including children, adolescents and pregnant women, so it is important to get specific recommendations from the provider when appropriate. In addition, caution must be taken if a

person has had heart attack, stroke or major heart surgery; for people in these situations exercise programs should be discussed with a physician, exercise physiologist or sports medicine expert.

Also, the interaction of exercise and the use of prescription insulin treatment in T1DM and advanced T2DM can be very complex and challenging for the patients. Unfortunately the default response for most patients is to avoid exercise if they use insulin to avoid these complexities. Because exercise is so effective at reducing blood sugar levels, regular exercise often reduces insulin needs in people with diabetes as much as 50% (this can mean fewer daily injections)! Also, regular exercise in a person with T1DM, can help prevent double diabetes, i.e. T1DM and T2DM. Instead of avoiding exercise if you are using extra insulin, find an experienced physician able to optimize insulin dosing around exercise.

Stress Reduction

Stress reduction techniques are often recommended to those with high blood pressure, however, the question is raised as to whether such techniques can have an effect on other cardiovascular concerns, as well as DM. In one study in people with T2DM, 108 participants were divided into groups receiving either a group diabetes education program with stress management training, or without for 1 year12. The researchers found only slight (but statistically significant) reductions in HbA1c in the treatment group. Another study used a technique called biofeedback as a means of stress reduction for patients with T2DM13. This study found significant reductions in blood glucose readings, HbA1c and muscle tension, as well as feelings of depression and anxiety.

Specific Dietary Factors

Glycemic Index/Glycemic Load and Fiber
There is evidence that, in addition to monitoring carbohydrate intake, consuming foods with a low glycemic index (GI) and/or glycemic load (GL) can be effective at keeping blood glucose better controlled. The GI is an indicator of how much of an impact a certain carbohydrate containing foods will have on blood glucose and insulin, including how quickly blood glucose raises following a meal. Foods with lower GI result in less fluctuation than foods with a high GI. The GL is the relationship between the GI and the amount of carbohydrate (in grams) in a serving of a specific food, so it can be more useful in determining not only how quickly blood sugar changes, but also the total change in blood glucose following a meal. A diet high in fiber may be helpful as well by slowing the glycemic index of meals consumed. High fiber foods tend to be low GI themselves, but also lower the GI of the entire meal when eaten with higher GI foods.

One study was conducted in 63 patients with T1DM, in which they were randomized to either a diet high in fiber, especially water-soluble fiber, (50 grams per day), or one low in fiber (15 grams per day) for 24 weeks. Incidentally, after analysis, it was found that the high fiber diet also contained lower GI foods than the low fiber diet. Those on the high fiber diet were encouraged to consume one serving of legumes daily, plus three servings of high fiber fruits and two servings of high fiber vegetables per day. The low fiber group was instructed to consume legumes only once per week, and to limit fruit and vegetable consumption to those with the lowest amounts of soluble fiber. At the conclusion of the study, it was found that those on the high fiber diet had a 24% reduction in daily blood glucose as compared to those in the low fiber group. Additionally, the high fiber group had lower HbA1C levels and fewer hypoglycemic episodes. The authors of the study concluded that “increased consumption of natural foods rich in dietary fiber and with a low glycemic index is both feasible and effective on blood glucose control in the long term”. 14

Vegan Diet
Another dietary approach that has been researched in regards to impact on DM is the vegan diet. A vegan diet is a diet style that eliminates all food from animal sources, i.e. no meat, dairy, eggs, etc. In a 2006 study, a low-fat vegan diet was compared to the American Diabetes Association recommended diet in people with T2DM17. The outcome measures compared were hemoglobin A1C, body weight, lipids (including cholesterol

and triglycerides) and urinary albumin (a measure of kidney function). Participants on the vegan diet were instructed to eliminate all animal products and to consume vegetables, fruits, grains and legumes. Both diets showed clinically significant reductions in hemoglobin A1C, body weight and urinary albumin excretion, as well as favorable changes in lipids. Both also tended to decrease blood glucose to the point that participants had to lower their doses of oral glucose lowering medications. However, the changes in the group following the vegan diet were substantially greater than those on the ADA diet. In fact, the authors of the study observed that the reduction in hemoglobin A1C in the vegan group (1.23%) is similar to that seen in studies of oral glucose lowering medications (1-2%)18. One of the reasons proposed for the superior benefits of a low-fat vegan diet is that this type of diet typically consists of fewer calories, which is associated with reductions in hemoglobin A1C. Also, insulin sensitivity is increased by shifting fat intake from saturated fat to unsaturated fat and by consuming a high fiber/low GI diet – all of which are characteristic of a low-fat vegan diet. The more favorable lipid levels can be attributed to several things typical of this type of diet, including elimination of dietary cholesterol, lower saturated fat and higher fiber. Notable as well, triglycerides are found to increase with high simple carbohydrate diets, and decrease with high fiber/low GI complex carbohydrate diets.

One might wonder, if making dietary changes can improve outcome measures in patients with T2DM comparable to medication, why are the medications so frequently prescribed? One reason is that when health care providers make dietary recommendations, they are not well adhered to by patients. One possible reason for this is the lack of follow up after making such recommendations. Studies have shown that these types of recommendations have much better adherence if providers reinforce recommendations with patients during frequent follow up visits in order to help them to overcome the difficulties associated with making such changes19. Also, unfortunately our food supply has more high glycemic index, processed foods than healthier choices. Until more people like you ask your favorite grocery stores and restaurants to sell more healthful foods, cooking at home with fresh "whole food" ingredients remains the best choice for health.

Cow's Milk

Epidemiologic studies have found an increased risk of T1DM among children who consumed cow's milk early in life.20,21 It has been postulated that ingestion of cow's milk results in the production of antibodies that cross-react with and damage pancreatic insulin-producing cells.

Other opinions suggest the correlation between the development of T1DM and cow's milk may be related to an improved immune response an infant receives from breast milk compared with cow's milk22, 23. In other words, the relationship between cow's milk and T1DM is that cow's milk doesn't cause T1DM, it just doesn't provide protection against it, whereas breast milk may.

However, other studies have found no association between ingestion of cow's milk and the risk of developing type I diabetes24, and a recent study found that a diet with high levels of dairy products may actually decrease insulin resistance syndrome in young adults.25

Advanced Glycosylation Endproducts (AGE) in Diet

Oxidation of food occurs during the cooking process in the presence of oxygen. One of the most common reactions occurs when carbohydrates react with proteins at high temperatures, however, oxidation of oils can occur as well. This process forms little chemical bridges or bonds that alter the way food is treated inside the body. The resulting particles are called advanced glycosylation endproducts or AGE. These products are absorbed into the body and can bind to receptors, thereby sticking to things within the body that they shouldn't stick to. High consumption of AGE in food appears to affect kidney function and blood vessel disease in people with DM. One part of their relationship with blood vessel disease involves the stimulation of inflammatory processes27, 28, 29. Of note, because AGE intake increases various receptors, or adhesion molecules, on the inner lining of the blood vessels, high AGE intake may have lasting effects beyond one isolated meal.

Nutrition researchers Goldberg et al. published the most comprehensive list of the AGE content of food in the literature and provided tables of food AGE content30. The foods with the highest AGE content include (in decreasing order): high fat foods, high protein foods (meat and meat substitutes including tofu), and finally carbohydrate-dense foods. Of the high fat foods, spreads including butter, cream cheese, mayonnaise and cooking oils have particularly high AGE content. For the high protein foods, the method of cooking was particularly important in determining AGE content with oven frying, deep frying and broiling producing the highest AGE content in food. Stewing, boiling, poaching and microwaving produced lower AGE content in foods. Processed foods, i.e. boxed and pre-cooked foods, had the highest AGE content for carbohydrate dense foods. The lowest AGE foods included low-fat dairy, vegetables and fruits.

Garlic and Onions

Most clinical trials involving garlic are studies of extracts and supplements rather than culinary garlic. Most of the interest in using garlic for patients with DM is in its proposed ability to decrease atherosclerosis and other cardiovascular risk factors. The trials that are available provide mixed results. A 1998 study in the Archives of Internal Medicine concludes that 900 mg of garlic powder per day is no more effective at lowering high cholesterol than placebo31. However, a more recent study suggests that many of the negative studies done on garlic supplements are due to poor bioavailability of active ingredients from the chosen supplements rather than ineffectiveness of garlic extracts in general32. This same study also noted some interesting differences in outcomes between the sexes in normal subjects, including decreased blood glucose in male subjects, while female subjects experienced an increase, as well as increased HDL cholesterol and decreased total cholesterol in females, while the opposite occurred in males. These results were unexpected and as of yet unexplained and warrant further research. Another study evaluated 41 male subjects who had mildly increased total cholesterol (220-290 mg/dL) and were treated with an aged garlic extract33. This study demonstrated a small but significant reduction in total cholesterol, LDL cholesterol and blood pressure after 6 months of treatment with the supplement. One small study of 19 participants compared the advancement of atherosclerosis in one group taking a statin drug and placebo to another group taking a statin drug and aged garlic extract34. The results showed that the group with the added garlic extract had a greater reduction in the advancement of atherosclerosis. A recent study involving patients with T2DM demonstrated that a time released garlic powder supplement reduced triglycerides and fasting blood glucose both in patients continuing their medications, and in those discontinuing them35. Blood glucose levels were lowered enough in the medication group to lead to hypoglycemic events and required a lowering of the medication dosages. Caution and careful monitoring are advised.

Onion extracts have also been shown to inhibit blood clot formation36 and to lower blood pressure in patients with hypertension.37 In addition, onions contain relatively large amounts of quercetin,38 a flavonoid compound that inhibits aldose reductase.39 Since aldose reductase inhibition has been shown to reverse diabetic cataracts and neuropathy, inclusion of onions in the diet of diabetics seems desirable.

Conventional Medication Therapies

Blood glucose lowering medications are often prescribed by doctors for people with diabetes.40, 41, 42 The most common medication prescribed at diagnosis for patients with DM is metformin. Metformin works by decreasing the amount of glucose made by the liver, and may help decrease insulin resistance throughout the body as well7. Although typically well tolerated, metformin does cause gastrointestinal side effects (nausea, cramping, gas) in 15-20% of people. In addition, approximately 7-8% of people on the drug get a metformin-induced deficiency of vitamin B12.

Another class of DM medications is the sulfonylureas, which brand names include Glyburide and Glipizide. These drugs work by increasing pancreatic insulin secretion7. The meglitinides are a similar class of medications, which basically have the same action as sulfonylureas, but with more rapid onset, making

them most appropriate to take just before a meal. This class includes Repaglinide and Nateglinide. Common side effects of sulfonylureas and meglitinides include hypoglycemic episodes and weight gain. The long-term value of sulfonylureas in diabetes treatment has been questioned, as the medications may stress an already overworked organ.42

Thiazolidinediones (TZDs) include pioglitazone (Actos) and rosiglitazone (Avandia). They are used to improve insulin sensitivity, particularly improving the ability of fat and muscle cells to use glucose.7 Side effects of TZD medications include weight gain, swelling/edema and worsening of heart failure in patients with more serious heart disease. Rosiglitazone has been recently associated with increases in heart attacks in people taking the medication, however these results are still debated. 41

Alpha-glucosidase inhibitors help to decrease the amount of glucose absorbed in the intestine after a meal; members of this family of medications include Acarbose and Miglitol.40

One draw back of glucose lowering medications is that all of them can lose their effectiveness after a few years of use.42 The number of glucose lowering medications is constantly growing, however, and several new medications are on the horizon.

Prescription insulin administration is another method of helping to control blood glucose levels, especially in T1DM, but increasingly common in T2DM43. Rapid acting insulins, usually given at mealtime, are Novolog and Humalog. Other mealtime insulins are simply referred to as "regular" and have brand names such as Humulin R and Novolin R. Intermediate acting, or basal insulins are Humulin N and Novolin N. These are used to provide steady, longer lasting levels of insulin. There are also longer acting basal insulins such as Levemir and Lantus. Short-acting and long-acting insulin are now being offered mixed together to reduce the number of daily injections. 43

No available medication lasts forever and medicine still lacks a "magic bullet" that fully protects us from our own dietary indulgences.

Other Strategies for Treating Diabetes and Preventing Complications

The above evidence suggests that appropriate goals in the management of diabetes include maintaining blood glucose levels as close to the normal range as possible, minimizing the adverse effects of free radicals by enhancing antioxidant defenses, reducing the glycosylation of proteins and avoiding the intracellular accumulation of sorbitol. However we do not have medications that accomplish all of these protective strategies. Yet a number of different interventions that are currently considered to be in the realm of "complementary and/or alternative medicine" have been shown to accomplish one or more of these goals. In addition, specific methods of preventing or treating diabetic complications (such as cardiovascular disease and neuropathy) have been identified. In most cases the amount of evidence for nutritional or herbal approaches to diabetes treatment is less than that available for approved medications. Yet because medications are often associated with significant side effects, many patients choose to pursue alternatives. All treatments for diabetes should come after imperative changes in lifestyle.

Nutritional Supplements

Chromium and Brewer's Yeast

Chromium is an essential nutrient in human health; it functions as a component of a molecule called glucose-tolerance factor (GTF), which occurs naturally in the body and enhances the action of insulin at the cellular level.44 Minor to moderate levels of chromium deficiency may be common in the United States. Tissue chromium levels were found to decline with age in Americans 45 but not in individuals living in other countries.46 One dietary survey revealed that 90% of American diets contained less than the minimum suggested daily intake for chromium.47 Because of farming techniques that fail to replenish trace minerals in the soil, the chromium content of food is probably lower than it was at the turn of the century. A variety of studies have shown that suboptimal ingestion of chromium is associated with an

increased risk of various factors linked with diabetes and cardiovascular diseases.
In a double-blind trial, daily administration of 200 mcg of chromium produced a significant reduction in 2-hour post-prandial glucose levels in elderly women with borderline glucose tolerance.48 Another study of elderly patients showed chromium supplementation significantly reduced plasma glucose concentrations during a glucose tolerance test and significantly improved glucose utilization.49 Treatment with 150 mcg/day of chromium for four months normalized glucose tolerance in four of ten elderly individuals with abnormal glucose tolerance.50 Administration of 150 to 1,000 mcg/day of chromium improved glucose tolerance in three of six people with diabetes. Chromium supplementation has been found to reverse not only glucose intolerance, but also severe neuropathy in individuals.51 A newer study found that the use of chromium early in the course of therapy in diabetics reduced the degree of insulin resistance.52

One study involving people found that chromium supplementation reduces oxidative stress, a key factor in the progression of diabetes.53 A different study found that chromium-enriched yeast supplementation in type 2 diabetics reduced oxidative stress and improved blood glucose variables.54 A study of patients with type 2 diabetes mellitus found that a combination of chromium picolinate and biotin improved glycemic control when added to a typical diabetes care program with hypoglycemic drugs.55 The researchers also concluded that these improvements could add to reduced costs in diabetes management over time. A pilot study at Yale also demonstrated that when DM patients on oral hypoglycemic medications took a combination of chromium picolinate and biotin in addition, they had better outcomes on their glucose tolerance tests, as well as improved triglyceride levels and HDL to total cholesterol ratios. Finally, another study of the same supplement used by patients with T2DM supported these findings showing decreases in HbA1C, LDL, VLDL and total cholesterol56.

Not all studies of chromium supplementation have been positive. A recent study in Western adults with T2DM demonstrated that the administration of 400 micorgrams of chromium had no effect of markers of blood glucose control or cholesterol57. This result may be due to the low dose used in the trial, or the relatively high chromium content of the diet in the population studied.

Niacin

As a component of GTF, niacin (nicotinic acid) plays an important role in carbohydrate metabolism. Many refined foods consumed by Americans are depleted of niacin. Grains and other foods that are “enriched” usually contain added niacinamide, which is capable of performing most of the functions of Vitamin B3, but which cannot apparently be converted by the human body into niacin. In addition, most vitamin supplements contain niacinamide rather than niacin. A small amount of supplemental niacin may therefore be necessary for some individuals to enable the production of adequate amounts of GTF.

In one study, 16 healthy elderly individuals received either 200 mcg of chromium, 100 mg of niacin, or both, daily for 28 days.59 Fasting plasma glucose levels and glucose tolerance were not affected by either chromium or niacin individually. However, the combination of chromium plus niacin produced significant improvements during a glucose tolerance test and a significant (6.8%) reduction in fasting glucose. This study suggests that a relatively low dose of supplemental niacin, when combined with chromium, improves glucose metabolism and may therefore be useful for preventing and treating diabetes.

There is evidence that both experimental diabetes and type I diabetes in humans are related to a depletion of nicotinamide adenine dinucleotide (NAD) within pancreatic beta cells, resulting in failure of oxidative metabolism and subsequent cell death. As precursors to NAD, niacin and niacinamide are apparently capable of preventing the depletion of NAD in pancreatic beta cells.65 Researchers have found that nicotinamide can protect vital pancreatic cells from diabetes-inducing factors.58

Because of its capacity to protect pancreatic beta-cell function, niacinamide has been studied as a possible treatment for newly diagnosed type I

diabetes, which is characterized by progressive destruction of beta cells.66 In a double-blind study, 16 type I diabetics received either niacinamide (3 g/day) or a placebo, beginning one week after the start of insulin therapy. Insulin was successfully discontinued in 85.7% of the patients taking niacinamide, compared to 55.6% of those taking placebo ($p<0.05$). Three patients treated with niacinamide for 18 months remained in remission for more than two years. Remissions of such long duration are extremely rare in type I diabetes. In another study, 14 children who were at high risk of developing diabetes (as determined by high levels of antibodies against pancreatic islet cells) received either niacinamide (150-300 mg per year of age per day, maximum dose = 3.0 g), while eight children at similar risk served as controls.67 All eight of the untreated children developed diabetes, compared with only one of the 14 children who received niacinamide ($p<0.001$). A recent meta-analysis of 10 randomized controlled trials concluded that niacinamide effectively preserves residual pancreatic beta-cell function in children with type I diabetes, when treatment is begun at the time of initial diagnosis. A new study found that nicotinamide helps prevents complications, especially infections, in type 2 diabetic patients.68 A study of nicotinamide found that supplementation with this compound had effects in the body that are similar to insulin in its ability to control blood sugar.69 A randomized, clinical study of children with type 1 diabetes mellitus found that the use of nicotinamide alone or in combination with vitamin E improved metabolic control in these patients.70

Niacin is also used to lower serum cholesterol and reduce the risk of cardiovascular disease in patients with or without DM, although usually at larger doses (such as 1-3 g/day). Although this treatment is often prescribed by conventional physicians, many doctors are reluctant to recommend high-dose niacin for patients with diabetes and high cholesterol because it will occasionally increase blood glucose levels in people with DM.60 A 2002 study confirms this by showing that, while improving lipid profiles in individuals, patients with DM who took niacin were required to increase their dosages of oral medications and insulin to overcome increases in HbA1C and blood glucose71. However, these increases were able to adequately compensate. The effect of high-dose niacin is variable and this vitamin has also been reported to reduce insulin requirements in some type I diabetics.61

Consequently, high-dose niacin is not contraindicated in patients with DM72, however, blood glucose levels should be monitored closely. Another approach might be to use an extended release (ER) form of niacin as demonstrated by Grundy et al73. Moderate doses of ER niacin (1000 or 1500 mg per day) were shown to significantly reduce triglycerides and increase HDL cholesterol in patients with DM who were also taking statin medications, without significantly effecting glycemic control.

Biotin

The B-vitamin biotin plays a role in the intracellular metabolism of glucose. Particularly beneficial are its effects on glucokinase (GK), a key factor in the proper regulation of glucose metabolism, and it has shown promise in the treatment of DM. In one small study, seven T1DM patients were removed from insulin therapy and treated with biotin (16 mg/day) or a placebo for one week. Fasting blood glucose levels rose significantly in patients given placebo, but decreased significantly in those treated with biotin.74 In another study, eighteen diabetic patients were given 9 mg/day of biotin for one month, while 10 other patients received a placebo. The mean blood glucose concentration fell by 45% in patients receiving biotin, but did not change in those given placebo.75

Biotin has also been used to treat diabetic neuropathy. Three patients with severe diabetic peripheral neuropathy received 10 mg/day of biotin intramuscularly (IM) for six weeks, followed by 10 mg IM three times a week for six weeks, then 5 mg/day orally.76 The treatment duration ranged from 64 to 130 weeks. Within 4-8 weeks of the start of treatment, painful muscle cramps, paresthesias and the ability to walk improved markedly, and restless leg syndrome disappeared.

Additionally, biotin has been shown to reduce triglycerides in patients with T2DM (as well as in people without DM)77.

Vitamin B6

Studies have shown that serum levels of pyridoxine (vitamin B6) are below normal in approximately one quarter of adult and pediatric patients with DM, and that most people with DM have lower levels than non DM subjects, even if not outside the reference range78,79. A study of experimentally induced DM in rats suggests an increased need for vitamin B6 in subjects with DM due to its involvement in metabolic reactions which are increased in these subjects80. As such, pyridoxine supplementation of patients with DM was shown to improve glucose tolerance in some studies81 but was without effect in others.82,85 In one study, pyridoxine administered at a dosage of 50 mg three times per day had no effect on blood glucose but reduced the concentration of glycosylated hemoglobin (HbA1c) by about 6% after six weeks.87 This finding suggests that vitamin B6 inhibits the glycosylation of proteins and might therefore help prevent diabetic complications.

This was seen in a controlled study that found that patients with diabetic polyneuropathy had a significant improvement in nerve conduction velocity after a combination regimen of vitamins B1, B6, and B12.85 Consequently, Vitamin B6 has been used to treat patients with diabetic neuropathy. Eighteen such patients received 50 mg of pyridoxine three times per day or a placebo for four months. Six (67%) of nine of pyridoxine-treated patients reported significant relief from neuropathic symptoms, compared with 4 (44%) of nine placebo-treated patients. This preliminary report warrants further study. 89 A study in children with T1DM found that a combination of folate and vitamin B6 significantly improved the health of the endothelium of the patients, which is a measure of disease progression.90

Supplementation of pyridoxine has been studied in cases of gestational DM also, as seen in one study of fourteen women who were treated with 100 mg/day of pyridoxine for 2 weeks. At the end of the treatment period, 12 of the 14 women no longer had gestational diabetes.83 The same dosage of vitamin B6 also produced a significant improvement in glucose tolerance in 13 women with late-pregnancy gestational diabetes in another study.84 Other studies have failed to confirm the beneficial effect of vitamin B6 on gestational diabetes. However, in one particular study, the women were hospitalized and confined to a sedentary existence 85. It is possible that a beneficial effect of vitamin B6 on glucose tolerance was counterbalanced in that study by a lack of activity.

Vitamin E

Several decades ago, Wilfrid Shute, M.D., a pioneer in vitamin E therapy, reported that vitamin E supplementation reduced blood sugar levels in some diabetics.91 This observation had been confirmed in some studies,92 but others failed to find a beneficial effect of vitamin E.93 More recently, in a double-blind, placebo-controlled study, administration of 900 mg/day of vitamin E for four months to T2DM patients significantly improved glucose tolerance.94 Vitamin E also inhibited glycosylation of proteins when administered at doses of 600 or 1200 IU/day; the higher dose was slightly more effective than the lower dose.95Additional newer research has also suggested other positive effects on DM from vitamin E supplementation. For instance, one study found that 1,000 IU daily supplementation of vitamin E led to improved circulation to tissues in patients with DM after three months.96 A significant body of evidence indicates that vitamin E may help prevent heart disease, one of the main complications of diabetes.97, 98 One study of tocotrienols (mixed forms of vitamin E) reduced total cholesterol by 30% and LDL by 42% in patients with T2DM99. The authors of the study suggest that the antioxidant effects of vitamin E help to reduce the oxidation of LDL particles. A recent study also found that vitamin E supplementation decreased several markers of thrombosis in patients with T2DM.100 A different study found that patients with T2DM given 600 mg per day of vitamin E had improvements in the health of nerves that control the functioning of the heart.101 A study found that 500 IU of vitamin E per day given to patients with type 2 diabetes reduced the levels of factors that increase the risk of developing vascular complications.102 An additional study found that 800 IU per day of vitamin E improved beta-cell function, increased plasma insulin, and may have decreased insulin resistance in 40 patients with T2DM who took the supplement for a month.103

Despite all of these studies suggesting benefit, Vitamin E still receives significant criticism in the literature. Much of this criticism is due to the findings of the HOPE trial, a large clinical trial that administered 400IU of alpha-tocopherol to over 3600 patients with diabetes; vitamin E showed no effect on cardiovascular or renal outcomes. Criticism of this study includes the low dose chosen and the form of vitamin E, i.e. alpha-tocopherol vs. natural mixed tocopherols.104

Magnesium

Serum magnesium concentrations have been found to be significantly lower in patients with DM than in healthy controls105, and poor control of DM is often associated with low serum magnesium (hypomagnesiumemia).106 Magnesium deficiency has also been found to be common in children with T1DM.107 The reduced concentrations of magnesium seen in patients with DM appears to result in part from increased urinary magnesium excretions.108 A newer study has found that a group of persons with T1DM had insufficient levels of magnesium dietary intake.109In fact, the diet of Americans at large tends to be low in magnesium. Dietary surveys have shown that 80-85% of American women consume less than the Recommended Dietary Allowance (RDA) for this mineral.110 Daily magnesium intake in two other studies was only about two-thirds of the RDA.111

One significance of magnesium deficiency is that it has been associated with insulin resistance and overall poor blood glucose control in elderly individuals who are borderline diabetic.112 Hypomagnesemia has also been shown to be more pronounced in individuals with diabetic retinopathy113 or cardiac complications114 than in DM patients without such complications. Low serum levels of magnesium have also been found to be associated with other complications of T2DM, such as the development of foot ulcers.115 In addition, a considerable body of evidence indicates that magnesium can prevent cardiovascular disease, for which diabetics are at increased risk.116 Thus, magnesium supplementation may be an important component of the overall treatment of many diabetics.

Magnesium supplementation has also been found to improve insulin sensitivity and insulin secretion in patients with T2DM117. A study of 62 subjects with T2DM who also had low serum magnesium levels showed that by correcting the deficiencies in these subjects with oral supplementation of a magnesium chloride solution, insulin sensitivity was improved, as were HbA1C and fasting glucose measures118.

Several studies have found significant evidence that magnesium intake is significantly associated with a reduced risk of developing diabetes also.119 A segment of participants in the Women's Health Study (a cohort of 39,345 U.S. women) were examined to determine the relationship between dietary magnesium intake and the development of DM120. These women had no prior history of cardiovascular disease or T2DM. The study found an inverse relationship between magnesium intake and future development of T2DM, with particularly increased benefits in overweight women. This suggests a protective role of increased dietary magnesium intake against the disease.

Vitamin C

Vitamin C is an antioxidant vitamin required for normal human defense to free radical damage; vitamin C also has a structural role in the formation of collagen, the protein latticework that forms the foundation for most structures in the body, including blood vessels.

People with DM are at increased risk of developing vitamin C deficiency. For example, the vitamin C concentrations in plasma, platelets,121 and white blood cells122 were significantly lower in subjects with DM than in healthy controls. Vitamin C deficiency in diabetic patients may be more pronounced within the cells than in plasma or other body fluids. That is because vitamin C is structurally similar to glucose, and may therefore compete with glucose for transport into cells. In the presence of elevated blood sugar, the uptake of vitamin C into cells appears to be impaired.123 This reduced entry of vitamin C into certain tissues may result in a kind of "localized scurvy." It is noteworthy that the vascular changes resulting from scurvy resemble those seen in diabetics.

In addition to maintaining the integrity of blood

vessels, vitamin C has been shown to inhibit three different biochemical processes that are associated with end-organ damage in diabetics. First, vitamin C functions as an antioxidant, thereby protecting vessels from oxidative damage. Second, vitamin C inhibits the intracellular accumulation of sorbitol. In one study, supplementation with 2,000 mg/day of vitamin C reduced red blood cell sorbitol accumulation by 56.1% and 44.5% in healthy individuals and those with DM, respectively.124 Third, vitamin C significantly reduced the glycosylation of proteins, when given to healthy volunteers at a dose of 1 g/day.125 Additionally, a study of 20 diabetic patients found that 500 mg of ascorbic acid given twice daily led to significantly increased levels of ascorbic acid in the blood and decreased the albumin excretion rate, a key measure of disease progression in patients with DM.126 A randomized, double-blind study of 30 patients with type 2 diabetes found that supplementation with 1250 mg of vitamin C per day slowed the progression of kidney disease that developed as a complication of DM.127 Blood sugar curves reflecting poor control were also seen in subjects with vitamin C deficiency; these values returned to normal after supplementation with vitamin C.128 A study of 56 outpatients with T2DM found that 2 grams per day of vitamin C led to improved glycemic control and fasting blood glucose levels in addition to having a favorable effect on cholesterol and triglycerides.129

Finally, a randomized, double-blind study of 30 patients with T2DM found that daily oral supplementation of 500 mg of vitamin C decreased arterial stiffness, which is an indicator of vascular disease130. The study also demonstrated a reduction of systolic blood pressure of nearly 10 mmHg, and diastolic pressure of 4.4 mmHg. These studies suggest that long-term supplementation with vitamin C may help prevent many of the complications of diabetes.

Vitamin B12

Cobalamin or Vitamin B12 is a member of the B vitamin family. B12 is a common nutritional deficiency as adults age and adults with diabetes may be particularly vulnerable because of medication effects as well as neurological changes affecting stomach acid production and the release of cofactors required for B12 absorption.

Injections of vitamin B12 have been used to treat retinopathy in patients with T1DM. In one study, 15 patients added 100 mcg of vitamin B12 to their daily insulin injection. After one year, all signs of retinopathy had disappeared in seven cases.131 Similar results were reported by others.132

Vitamin B12 has also been used to treat diabetic neuropathy. While several studies from the 1950's show improvement in neuropathy with vitamin B12 supplementation133, there are no recent studies supporting this. In one study, 12 patients received 15-30 mcg/day of vitamin B12 by injection for the first 7-14 days, followed by 15-30 mcg, 1-2 times a week.134 Seven patients had complete or almost complete remission of the neuropathy and three had partial improvement. The response appeared to depend more on the frequency of the injections than on the amount of each individual dose.

High serum levels of homocysteine (hyperhomocysteinemia) are considered a risk factor for cardiovascular disease. Research has shown that hyperhomocyteinemia is associated with both the hyperinsulinemia seen with insulin resistance and increased urinary albumin excretion. It is also associated with low serum levels of vitamin B12135. Interestingly, however, supplementation with vitamin B12 has resulted in lowering homocysteine levels, but as failed to show subsequent reductions in incidence of cardiovascular disease136. The patients included in this study had long-standing cardiovascular risk factors, so short-term improvements in homocysteine appear to not offset long-term risk. The value of prevention of hyperhomocysteinmia has yet to be determined.

Copper (Cu)

Copper is an essential mineral in human nutrition. Although copper has many functions, one function of note in diabetes is as a cofactor in the function of superoxide dismutase, a potent antioxidant defense enzyme. The typical American diet contains only about half of the Recommended Dietary Allowance (2 mg/day) for copper,137 thus deficiencies of this mineral may be common. Two male volunteers who consumed a controlled intake of 0.7-0.8 mg

of copper per day for 5-6 months had increased 138 glucose levels during a glucose tolerance test. These levels returned toward normal after adequate amounts of copper were restored to the diet. In two other volunteers, administration of 6 mg/day of copper improved glucose tolerance, suggesting that their usual diet was deficient in copper.139 A study in patients with T2DM found that those with progressive kidney disease (a complication of DM) excreted higher levels of copper in urine and had lower levels in plasma than patients with less serious disease.140

Potassium (K)

Potassium is a critical electrolyte in human health; potassium is required for every nerve transmission in the human body and is critically important to maintaining normal heart rhythm and blood pressure. In addition to its functions in the nervous system, potassium appears to influence protein and glucose metabolism. Obese patients undergoing a protein-sparing modified fast without potassium supplementation had a striking reduction in peripheral glucose utilization and insulin levels. These changes were reversed by potassium supplementation.141 In addition administration of potassium to children with protein-energy malnutrition resulted in rapid improvement in the insulin response to an intravenous glucose load.142 Potassium supplementation also prevented the impairment of glucose tolerance that sometimes results from treatment with thiazide diuretics (often used to treat high blood pressure). 143 These studies indicate that potassium plays an important role in glucose metabolism. The beneficial effect of a high-fiber diet on glucose metabolism may be due in part to the relatively large amount of potassium present in fruits, vegetables, and other high-fiber foods.

An additional study found that potassium levels in the body are critical to the stability of potassium ion channels, which are vital to the health of blood vessels.144 Sufficient potassium intake may help reduce vascular complications from diabetes, if only by improving high blood pressure.

Zinc (Zn)

Zinc is an essential mineral in human nutrition and is required for normal immune function, has antioxidant action and is required for normal blood vessel response to changes in blood flow. The typical American diet is low in zinc. In one dietary survey, 68% of adults consumed less than two-thirds of the RDA for zinc.145 A controlled study of 50 humans with DM found that zinc levels in the blood were significantly lower than in normal individuals146. A recent 2007 epidemiologic study found that people with T2DM with low blood zinc levels had a higher risk for coronary events like heart attack and stroke. 147

Plasma zinc concentrations were reduced and urinary zinc excretion was elevated in diabetic patients.148, 149 Zinc plays a role in the synthesis of insulin by pancreatic beta cells150 and in the action of insulin at the cellular level.151, 152

A group of 15 patients with diabetic neuropathy that were given 660 mg of zinc sulfate daily for six weeks had significant improvement in both fasting and post meal blood sugar levels and in nerve conduction velocity tests.153

A newer study found that supplementation with 30 mg daily of zinc for six months, either alone or combined with chromium supplementation, led to improvement in at least one measure of disease progression.154 Another newer study confirms that zinc can lower blood glucose, as well as reduce toxic effects throughout the system in diabetic subjects.155 An additional study found that oral zinc supplementation reduces blood sugar in diabetic patients with high blood sugar and stimulates more efficient glucose metabolism, especially in muscle tissue .156 A new study of diabetic patients in Tunisia found zinc supplementation prevents some of the negative effects of oxidative stress that occur in these patients.157 These data suggest that zinc supplementation may be especially important for patients with DM.

Selenium (Se)

One study found evidence that patients with T2DM have lower levels of selenium in the blood.158 In another study, a group of pregnant women with T1DM were found to have an inverse association between serum selenium concentration and the degree of visual impairment found in

these patients.159 A more recent study found that selenium reduces insulin resistance in the body, thus making insulin more effective in reducing blood sugar.160 Other newer research indicates that selenium mimics the action of insulin.161 It may do this by activating key proteins that are also activated by insulin. An additional study found that selenium has powerful antioxidant effects against oxidative stress in diabetic patients.162 More research found that selenium supplementation improved blood sugar and fat metabolism in patients with T2DM.163

As always in science, findings are often conflicting. Of interest, a recent study testing the impact of selenium on skin cancer prevention found a higher incidence of diabetes in the group of the study that was taking selenium! 164 Participants were taking 200 micrograms per day for an average of 7.7 years. This finding is also supported by epidemiologic research findings that patients with DM had higher blood selenium levels. 165

To date there is no data supporting selenium for the prevention of diabetes, and the optimal intact of selenium for people with diabetes remains to be established.

Thiamine

Thiamine (B1) is a member of the B vitamin family. Blood thiamine concentrations were significantly lower in subjects with T1DM than in healthy controls, although the levels in T2DM subjects were normal.166 Thiamine has been found to play a large role in the proper regulation of glucose metabolism and pancreatic beta-cell function.

A study of a mixture compound consisting of thiamine, arginine, caffeine, and citric acid found evidence that this formulation reduced body weight, improved fat metabolism, and improved blood sugar levels in diabetic subjects.169 In another study, administration of 10 mg/day of thiamine for four weeks reduced blood glucose levels and urinary excretion of glucose in six (54.6%) of eleven patients with DM.166 A more recent study of 10 children with T1DM found that a form of thiamine administered for three months led to improved metabolic control in the children.168

Also, thiamine, in combination with other B-vitamins, has recently been tested as a treatment for diabetic neuropathy. Twenty-four patients received daily doses of either a placebo or 320 mg of allithiamine (a lipid-soluble derivative of thiamine found in garlic), plus 720 mg of pyridoxine (vitamin B6) and 2.0 mg of vitamin B12.167 After two weeks, the dosages of the vitamins were reduced by about two-thirds. After 12 weeks of treatment, there was a significant improvement in nerve-conduction velocity in the vitamin-treated group compared with the placebo group, and no significant side effects were seen.

Vanadium

Vanadate, an oxidized form of the trace mineral vanadium, appears to have an insulin-like action.170 A study found that administration of vanadyl sulfate (another form of vanadium) at a dose of 50 mg twice daily for four weeks to patients with T2DM reduced the mean blood glucose concentration significantly by about 20%.171 Other research has found beneficial effects from vanadium in both T1DM and T2DM.172 A new study of subjects with DM has found that a formulation of vanadium, molybdenum, and some other metal complexes has strong blood sugar lowering-properties.173

Another study was conducted in 16 people with T2DM174. Some of the outcome measures included fasting blood glucose, insulin sensitivity, HbA1C, glucose production by the liver and lipid levels. These measurements were taken after administering vanadyl sulfate at doses of 75mg, 150 mg and 300 mg. The 150 and 300 mg dosages both demonstrated a significant decrease in HbA1C, as well as in increase in insulin sensitivity. A significant reduction in fasting blood glucose was only seen at a dosage of 300 mg, as was a reduction in serum cholesterol, however, this was associated with a decrease in HDL (beneficial) cholesterol. There was no change at any dosage in triglycerides or apolipoprotein A or B (other indicators of cardiovascular disease), nor in glucose production by the liver. The therapeutic dosages were also associated with some gastrointestinal symptoms, including cramping and general abdominal discomfort. All of the people at the 300 mg dosage experienced diarrhea, which required

treatment for resolution. The authors of the study suggest that long term studies need to be conducted in order to determine if vanadium supplementation will benefit patients with DM long term. They also state that the gastrointestinal symptoms associated with vanadium makes further study with higher doses difficult, and they suggest that this may be overcome by administering gradually increasing dosages.

In yet another study, 6 people with T2DM received 200 mg of vanadium sulfate per day for 3 weeks, in addition to their conventional treatment with sulfonylureas and dietary suggestions.175 This study found a significant improvement in fasting plasma glucose and HbA1C, although there were no improvements noted in the plasma glucose and insulin response levels in the people during an oral glucose tolerance test. People in this study also experienced gastrointestinal symptoms including nausea, diarrhea, abdominal cramps and a dark discoloration of the stool (although no signs of GI bleeding were present).

Of note, there is no convincing evidence that vanadium is an essential mineral in human nutrition, therefore for now, all actions of supplemental vanadium are considered pharmacologic. Vanadium is currently being promoted in the popular press and by some physicians as an effective treatment for diabetes. However, it should be noted that the dose of vanadium used in the study mentioned above was several thousand times as much as that found in a typical diet. There is no precedent for using such large amounts of a trace mineral, and there are concerns about the potential toxicity of such large doses. Vanadium accumulates in the body with long-term use, and toxic effects of this trace mineral have been reported in animal studies.173 Until long-term safety studies are done with humans, high-dose vanadium cannot be recommended as a treatment for diabetes.

CoQ 10

Coenzyme Q10 (referred to as CoQ10) is an important part of the electron transport chain (ETC) found in the mitochondria of cells in the body. The ETC is responsible for producing molecules that the body uses for energy. CoQ10 has been shown to inhibit damaging oxidation that takes place in cells, in fact it is considered to be a very potent antioxidant, including reducing the susceptibility of LDL cholesterol to oxidation 177,178. Some studies have noted deficiencies of CoQ10 in patients with DM, and have found this to be associated with increased oxidative stress. 179 It has even been suggested that a deficiency of CoQ10 could contribute to decreased functioning of the pancreatic beta cells49. Some studies have shown that low CoQ10 levels are associated with poor blood glucose control as well as with diabetic complications180.

One study of 40 patients with T2DM reports administration of 200 mg per day of CoQ10 for 12 weeks181. This study showed improved endothelial function (a marker of oxidative damage), however, lipids, blood glucose control and blood pressure were not affected in this study. Another study enlisted 74 people with uncomplicated T2DM as well as dyslipidemia (altered blood lipids) and administered 200 mg per day of CoQ10 for 12 weeks182. This study found a significant reduction in both systolic and diastolic blood pressure, as well as a reduction in HbA1c..

Alpha Lipoic Acid

Alpha-lipoic acid (ALA) is a potent antioxidant in the human body, and a critical cofactor in normal metabolism (energy production).

A study of alpha-lipoic acid (ALA) administered to patients with DM has found that this compound has many properties and effects similar to those of insulin.183 As such, a different study found that ALA improves the sensitivity of insulin action in the body.184 A new study of an oral time-released formulation of ALA in people with DM found that blood sugar levels were significantly lowered over a six-week period 185, and other studies are supporting this in that ALA was found to improve glucose regulation in patients with T2DM186. Other studies have found that ALA can reduce and prevent oxidative stress damage in people with DM.187

ALA is currently being used to improve symptoms of diabetic neuropathy, as demonstrated by a controlled study of 12 patients with T2DM, which

found that daily administration of 600 mg of ALA led to improvement in a variety of neuropathic symptoms such as numbness, pain, and burning.188 A recent study of 181 DM patients was conducted comparing increasing doses of ALA with placebo in ability to decrease subjective symptoms of neuropathy, including pain, paresthesia and numbness, as well as objective measures of muscle strength and sensory function189. Patients were given oral doses of either 600, 1200 or 1800 mg daily of ALA or placebo for 5 weeks. There was no statistically significant difference in response rates between all ALA groups (all being >50%) whereas the response rate in the placebo group was 26%. Favorable responses in the ALA groups were seen in pain reduction, muscle strength and sensory function. A clinically relevant improvement in outcome measures was seen within 2 weeks in the ALA groups. It is important to note, however, that there was also a dose dependent increase in nausea in the ALA groups, with additional symptoms of vomiting and vertigo in the 1800 mg group No one in the 600 mg group had to withdraw from the study due to severity of side effects, whereas they did in the higher dose groups. The authors of the study state that it is not clear whether the improved measures indicate that the treatment is slowing the progression of neuropathy, but they state that the improvement in sensory function does suggest this improvement. The authors also state that since there is no additional benefit seen with increasing doses, that 600 mg per day is sufficient as treatment of neuropathy.

Evening Primrose Oil

One study conducted with 111 patients with mild diabetic neuropathy were randomly assigned to receive 12 capsules per day of evening primrose oil or placebo for 1 year in double-blind fashion.190 Evening primrose oil was significantly more effective than placebo, as determined by various objective measurements of nerve function.

N-Acetyl Cysteine (NAC)

N-Acetylcysteine is a precursor to the antioxidant glutathione. Glutathione is a small protein that functions to reduce many different types of free radical damage. One study reports that certain vascular adhesion molecules (implicated in atherosclerosis) are higher, and reduced glutathione (a very potent antioxidant found in the body) is lower in patients with DM than in healthy controls191. In this study, when patients with T2DM were given NAC orally for 1 month. Adhesion molecules decreased and glutathione increased, suggesting that increased antioxidant potential in the body may reduce risk for cardiovascular damage. This increase in glutathione was also seen in red blood cells of people with T1DM in a later in vitro study192.

NAC has also been shown to be useful in treating patients undergoing dialysis due to end stage renal failure – the most common reason for which is diabetes. A 2007 study showed that IV acetylcysteine decreased plasma homocysteine (mentioned earlier as a risk factor for cardiovascular disease), and also increased endothelial function 193.

L-Carnitine

L-carnitine is an amino acid required for the normal metabolism of fat for energy. In a study of L-carnitine, 35 people with T2DM were divided into two groups and received either 1g three times a day of L-carnitine, or placebo for 12 weeks194. The investigators determined that L-carnitine significantly lowered fasting blood glucose, although it had no effect on HbA1C. Of note was that some people had quite substantial decreases in fasting blood glucose (up to 17%), while others showed much more modest decreases. They also found that triglycerides were increased the test group. Earlier studies had shown both an increase and a decrease in triglycerides from L-carnitine administration.

Other studies indicate that L-carnitine is also effective in treating diabetic neuropathy. It is shown to decrease pain, improve the regeneration of nerve fibers and improve sensory function in patients with diabetic neuropathy when administered at a dose of 1,000 mg three times a day for 52 weeks195.

Vitamin D

Vitamin D is really more of a hormone than a vitamin. Vitamin D has been historically thought of as important only to bone health and calcium absorption, however research has accumulated over

the past decade that vitamin D also has important functions in cancer prevention and glucose regulation. A recent study demonstrates that vitamin D levels are lower in patients with T1DM than in healthy people195, and an earlier study in rats shows that vitamin D dependent calcium influx is necessary into pancreatic beta cells in order for them to secrete insulin196. Another study was conducted in people without diabetes 65 years old and older197. These people were given daily doses of 500 mg of calcium citrate and 700 IU of vitamin D3, or placebo, for 3 years in an attempt to investigate the effects of supplementation on bone health in this population. Incidentally, it was found that 92 of these people had impaired fasting glucose. Those in the treatment group showed a slower increase in fasting blood glucose and less insulin resistance than the placebo group.

One study in pregnant women showed a decreased risk of the development of T1DM in their children if they had supplementation of cod liver oil (CLO) during their pregnancie198. This protective effect is may be due to the high vitamin D content of CLO, its high content of the omega 3 fatty acids EPA and DHA, or both.

Omega 3 Fatty Acids

Dietary fat content can have an impact on cardiovascular risk scores. There is much interest in determining what types of dietary fats, if any, might be helpful in reducing these risk scores. In addition to possibly having a protective effect in the development of T1DM, fish oils, and particularly two kinds of fats in fish oil known as EPA and DHA, are proposed to have the ability to do so. They are particularly known for lowering triglycerides in patients with DM who have elevated levels.199 One study in T2DM patients showed that meals combining monounsaturated fats with EPA and DHA could lower the rise of a particular subclass of fat with a high atherogenic potential, as well as improve measures of vascular function, when blood tests were done following the meals. 200 Another study shows that supplementation of 1,800 mg daily of EPA decreased the progression of a marker of atherosclerosis. 201 The authors suggest that this could indicate that supplementation with EPA would be useful in the primary prevention of atherosclerosis, particularly in patients with DM. Still another study in patients with T2DM suggests that fish oil supplementation in people who don't have elevated triglycerides could lead to a small increase in fasting blood glucose, due to the shift to preferentially utilizing fats rather than carbohydrates for energy.202 This slight elevation in FBG, however, didn't lead to an increase in HbA1C.

Herbal or Plant Products Studied for Use in DM

Pycnogenol®

Pycnogenol® is a French maritime pine bark extract (Latin name Pinus maritima). It has been shown in some studies to have potent antioxidant activity203, which has prompted interest in studying its effectiveness in treating retinal complications in DM, as well as retinal vascular complications associated with other disorders. It is thought that in these situations, antioxidants can be useful in preventing the pathological blood vessel formation and edema, which are two of the causes of visual deterioration in retinopathies.

One study of Pycnogenol® was done in twenty patients who had retinopathy associated with various disorders, including atherosclerosis, DM, high blood pressure or thrombosis of a vein in the retina204. Patients were place in either a treatment group, and given 50 mg of Pycnogenol® orally 3 times per day for two months, or they were placed in a placebo group. Visual deterioration associated with retinopathy is progressive, and as such, the placebo group demonstrated worsened visual acuity. In the Pycnogenol® group, the deterioration was either slowed, or improved. An exam was performed to determine the health of the back of the eye internally (the fundus). There was improvement noted in the treatment group, but not the placebo group. Other improvements noted in the Pycnogenol® group were improvement in vasculature of the retina, as well as metabolic and physiological function.

In another study, Pycnogenol® was shown to also improve fasting blood glucose levels, as well as measures of vascular health205. The study involved seventy seven patients with T2DM, 34

of which were given 100 mg Pycnogenol® orally per day, and 43 of which were given placebo. All participants were also concurrently taking oral blood glucose lowering medications, as such, improvements in outcome measures were also seen in the placebo group, however, the treatment group showed significantly greater improvements.
A recent study also showed a decrease in measures of microangiopathy (dysfunction of small blood vessels) in the feet of patients with DM who were given 50 mg Pycnogenol® 3 times per day206. A decrease in these measures could indicate a decrease in the incidence of ulcerations of the feet.

Trigonella foenum graecum (Fenugreek)
Fenugreek seed (Trigonella foenumgraecum) is an annual plant of the leguminous family. Fenugreek seeds are commonly used as a condiment in India. Yemenite Jews have traditionally used fenugreek to treat T2DM. In a study involving 10 people with T1DM, isocaloric diets were consumed with or without 100 g/day of debittered, defatted fenugreek-seed powder, each for 10 days in random order.207 The powder was divided into two equal doses and incorporated into bread. Compared with the control diet, the mean fasting plasma glucose concentration was significantly lower by 28% and glucose tolerance was significantly better during fenugreek treatment. Serum total-and LDL-cholesterol levels were also significantly reduced by fenugreek. Similar results were achieved with a lower dose of fenugreek seeds.208 A newer double-blind, placebo-controlled study involving 25 patients diagnosed with T2DM found that 1 gram per day of fenugreek led to improved blood glucose control and decreased insulin resistance.207

A new study has found further evidence that fenugreek can improve cardiovascular factors in people with diabetes.209 A new double-blind study of fenugreek found that this compound improves blood sugar control and reduces resistance to insulin in the body.210 The researchers found that the group receiving fenugreek had a significant improvement in these areas compared to a control group that only received the typical regimen of dietary control and exercise.

Aloe
The dried sap of the aloe plant is used as a traditional remedy for DM in the Arabian peninsula. Administration of one-half teaspoon daily for 4-14 weeks to five patients with T1DM resulted in a mean reduction in serum glucose from 273 to 151 mg/dl ($p<0.05$).211

Arctium lappa (Burdock Root)
Burdock root has been used traditionally in cases of skin eruptions, gout, and rheumatism. It is commonly used in Japanese cooking. In an uncontrolled study, administration of burdock root in doses of 54-81 g/day reduced insulin requirements in several diabetics. This effect disappeared when the treatment was discontinued; resumption of Burdock root again reduced insulin requirements.212

Momordica charantia (Bitter Gourd)
The fruit of Momordica charantia (Bitter Gourd) has been used in traditional herbal medicine for the treatment of rheumatism, gout, dysmenorrhea, jaundice, and disorders of the liver and spleen. Administration of 230 g/day of momordica for 8-11 weeks to a group of nine patients with DM, significantly improved the results of oral glucose tolerance tests.213

Cinnamon
There has been a lot of information presented lately on the blood glucose lowering effects of cinnamon, and the research literature appears to provide conflicting information. One study conducted in post menopausal, obese women with T2DM found that 1.5 g of cinnamon supplementation per day did not have an effect on fasting blood glucose, HbA1C, insulin resistance measures or lipid profiles214. In a study, by Blevins et al., 42 people with more diverse backgrounds were studied, and the findings were that oral cinnamon supplementation at a dose of 500 mg twice per day had no significant effect on fasting blood glucose, HbA1C, lipids or insulin levels215. Interestingly, the authors of this study speculate that perhaps cinnamon supplementation has different effects in different populations, with consideration being given to not only ethnic background and age, but to types of medication used, dietary habits and initial FBG and HbA1c levels as well.

One of the studies showing positive results with

cinnamon supplementation was conducted in 2003 in 60 people with T2DM216. People were divided into one of six groups: those receiving 1g, 3g, or 6g of cinnamon daily, or those receiving placebo capsules divided into three groups to correspond to the same number of capsules in the test groups. After 40 days, the investigators report large reductions in fasting blood glucose, total cholesterol, LDL cholesterol and triglycerides, with no effect on HDL cholesterol. A 2006 study in T2DM patients using an extract of cinnamon with the equivalent dose of 1g three times per day, also showed a significant reduction in fasting blood glucose, but reported no changes in HbA1c or lipids217. The authors of this study suggest that patients with poorly controlled DM (HbA1c>7%) may benefit most from supplementation with cinnamon.

Pomegranate Juice

Pomegranate juice is known to be high in antioxidants, and so has generated interested in the possibility of its ability to reduce measures of cardiovascular disease. In a study of 45 people with coronary heart disease (CHD), consumption of 240 mL of pomegranate juice daily for 3 months was associated with an increase in the blood flow to heart muscle, and consequently, lowered incidence of ischemia79. In this study, there were no negative effects on fasting blood glucose or HbA1c. Another study in patients with T2DM who were given 50 mL of pomegranate juice per day for 3 months showed significant antioxidant effects, including an increase in glutathione, without adversely effecting blood glucose control measures80. While it is encouraging that these studies showed no adverse effects in blood glucose control, it is important to avoid juices with added sugar content in those with DM.

Ginseng

Panax ginseng, commonly known as Chinese ginseng, has a long history of use in Asian countries as a tonic. It is used in China to treat diabetes. At least five constituents of this herb have been shown to exert hypoglycemic effects.

Panax quinquefolius (American ginseng) grows in the United States and seems to have different properties than Panax ginseng. A study of 9 people with T2DM found that 3 grams of American ginseng administered 40 minutes before an oral glucose challenge significantly reduced blood glucose levels compared with controls. 220 In a different study, 10 men and women with T2DM found that 3 grams of American ginseng led to blood glucose reductions after eating and was as effective in lower these levels as 6 and 9 gram doses. 221 A study conducted in healthy individuals, without DM, showed a significant decrease in blood glucose after its ingestion in an oral glucose tolerance test when the participants were given Panax before the test. The study was conducted with 3 different doses of Panax, 1, 2 or 3g, but didn't show a difference in effect with increasing doses. 222 In this study, timing of the ginseng ingestion was not as significant as in the other study. Patients who took ginseng before or with the meal had equal blood sugar regulation benefits.

Morus indica (Mulberry)

Mulberry leaves have been shown to have some anti-diabetic properties. A study of 24 people with T2DM found that patients who received a compound derived from mulberry leaves had significant improvement in blood sugar control compared to a group that received glibenclamide, a commonly-used drug in the treatment of T2DM223. In addition, the researchers discovered that a variety of blood lipid factors, such as total cholesterol, LDL and HDL cholesterols, triglycerides and plasma free fatty acids, were improved in the mulberry group. This is an important consideration in people with diabetes because of their increased vulnerability to cardiovascular disease.

Gymnema sylvestra

Gymnema is native to Africa and India, and has been used traditionally in Auyervedic medicine to treat DM. It is believed to reduced one's ability to detect sweetness on the palate, and has also shown in test tube studies to increase pancreatic beta cell function225.

One study in people with T1DM monitored glucose control measures in people taking 200 mg of gymnema twice a day. They were found to have significant reduction in both fasting blood glucose and HbA1c, and their required insulin doses were decreased226.

Another study in T2DM patients who were taking sulfonylureas, additionally were administered 400 mg daily of gymnema227. This study also reports reductions in HbA1c and fasting blood glucose, as well as lipids. In this study, many patients were able to reduce dosages of their sulfonylurea medications, and 5 patients were even able to discontinue them.

Cocoa

The recent news that cocoa may provide health benefits is certainly exciting to many, particularly those who thoroughly enjoy chocolate. One reason for the potential health benefits is their flavonoid content, including catechin; catechin is one of the flavonoids found in tea that is found to have great antioxidant potential. One study involved a comparison of a typical American diet to this typical diet, plus the addition of 22 g of cocoa powder and 16 g dark chocolate daily for 4 weeks. 228 The diet with the addition of cocoa powder and chocolate was found to decrease the oxidation of LDL cholesterol, to increase HDL cholesterol and to increase total serum antioxidant capacity. In another study, 44 participants with pre-hypertension (high blood pressure) or untreated stage 1 hypertension, without other cardiovascular risk factors, were divided into 2 groups to either receive 6.3 g per day of dark chocolate or white chocolate. 229 After 18 weeks, the dark chocolate group was found to have significantly lower blood pressure readings as well as increased markers of vessel health. Another study in patients with early hypertension also compared dark chocolate, at 100 g per day, with white chocolate, at 90 g per day, for 15 days. 230 This study found significant reductions in blood pressure, LDL cholesterol and markers of inflammation. This study also found improvements in insulin resistance and blood glucose measures in an oral glucose tolerance test.

Traditional Chinese Medicine and Acupuncture in Diabetes

In Traditional Chinese Medicine (TCM), there are three main causes of DM: improper food intake (fat, alcohol, and sweets), emotional impairment (stress and anxiety) or sexual stress. Any of these may result in one of the following three distinct syndromes (italicized terms refer to the TCM diagnosis, which frequently differs from the Western use of the term):

1) The Upper Jiao type of diabetes is related to a lung deficiency. In TCM the function of the lung is to control breathing and to dominate qi (energy, pronounced "chi"). This lung deficiency results in a fluid deficiency, and the prevalent symptom is great thirst.

2) The Middle Jiao type of diabetes, is related to the spleen. The spleen in TCM is synonymous with both the adrenal gland and pancreas of Western medicine. This deficiency leads to symptoms of great hunger.

3) The Lower Jail type of diabetes relates to the kidney. The function of the kidney in TCM is to dominate water metabolism. The kidney in TCM relates both to the kidney and the reproductive organs in Western medicine. Kidney deficiency leads to symptoms of great urination.

Chinese Herbal Formulas

Long-established systems of traditional medicine have evolved from recordings of human experience. Although not based on concepts of modern Western science, they are founded on a body of organized knowledge and have provided useful treatments for thousands of years. Chinese herbal formulas usually consist of a combination of individual herbs that are believed to have synergistic effects. Unfortunately there are very few clinical trials in humans of traditional Chinese herbal formulas published in English in Western journals. However, there are substantial references to Chinese herbal formuals that have been studied in animal models of diabetes suggesting benefits.231-235

Acupuncture

Traditional Chinese acupuncture treatments have been shown to relieve the pain associated with diabetic neuropathy.236 A study of 55 patients with T1DM found that 10 sessions of acupuncture treatment led to improved circulation in the lower extremities of 78.2% of cases.237 A study in diabetic rats found that electroacupuncture can induce a sustained reduction in blood sugar levels.238 A study of 46 patients with painful, chronic neuropathy in the limbs underwent six courses of TCM acupuncture points over a period of 10 weeks.239 During a one-year follow-up

period, 77% had significant improvements in symptoms. One pilot study compared TCM acupuncture with Japanese acupuncture in patients with diabetic neuropathy240. Both forms of acupuncture lowered pain scores, whereas TCM acupuncture was also found to improve nerve sensation tests.
Another study involving forty-four patients with painful diabetic neuropathy showed that 34 patietnts (77%) had significant improvement in symptoms241. Many of these patients were able to discontinue or significantly decrease their pain medications, with results lasting at a 52 week follow up.

Emerging Approaches

- Capsaicin, a constituent of red pepper, has been studied for use with diabetic neuropathy. This can be a very painful complication for those with DM, and it has been proposed that capsaicin can help alleviate this pain. A pilot study of 13 people with diabetic neuropathy was done in which capsaicin cream was applied to the feet242. The study reported significant reductions in pain, as well as some improvement in temperature sensation.

- High doses of aspirin may counteract some of the negative effects of insulin resistance. The researchers warn that such high doses have detrimental effects, but these new findings may help develop safer therapies in the future. A 2007 study finds that 100 mg of aspirin daily can reduce the incidence of vascular events in patients with peripheral artery disease by 26% over 2 years, and concludes that it should be taken in those with DM 243.

- A study in JAMA found that a couple of alcoholic drinks per day may prevent DM in older women. The women in the study were at high risk for developing DM and received a controlled diet. The women were compared to a similar group of who consumed orange juice with no alcohol. The researchers cautioned that additional research is needed before alcohol can be recommended in persons at risk for developing DM. One study conducted in people without DM showed increase insulin sensitivity in those who had a low to moderate daily intake of alcohol244. Another study in people with DM shows that those who had a low daily intake of alcohol (<12 g per day) had a 47% decreased risk of developing acute coronary syndrome when compared to those with no alcohol intake245.

- Probucol, a drug developed as a cholesterol-lowering agent, is also found to have antioxidant effects and has been shown to decrease the progression of kidney disease in those with DM246.

- Benfotiamine is a specially formulated fat-soluble form of vitamin B1 (Thiamine). It has been shown in studies to be effective in treating diabetic neuropathy247. A recent study also showed that when given to DM patients consuming diets with high AGE contents, it was shown to be protective against the vascular dysfunction that can accompany such meals248.

- Bariatric surgery is gaining popularity as an option for weight loss. Bariatric surgery typically involves either reducing the capacity of the stomach by stapling its walls, or rerouting the digestive system to reduce digestion and therefore absorption of calories (and also nutrients). Although bariatric surgery results in dramatic weight loss, it causes other problems including gastrointestinal side effects of gas, cramping, diarrhea and malabsorption of nutrients. Due to the dramatic reduction in body weight, and the induction of relative starvation by malaborption and reduced digestion, bariatric surgery appears to dramatically improve insulin resistance and lead to reversal of diabetes in some patients.251

- Stem cell research offers hope for a wide variety of autoimmune and chronic diseases. Specifically in diabetes, stem cell research may offer cures to T1DM and T2DM through the regrowth of damaged beta cells in the pancreas.

Conclusions

Diabetes of all types is a complex disease that requires the dedication of of a team to treat, including the person with the disease. Understanding diabetes, its risk factors and the measurements used to evaluate the progression on the disease can help control the disease. Lifestyle, including diet, exercise, not smoking, and reducing stress are the most important elements of

successfully avoiding the complications of diabetes. In a chronic disease without a cure, all treatments, conventional medications and alternative therapies, have a role in treating the disease; as a culture with increasing rates of diabetes and a medical system with fewer and fewer effective options we are not at a place where we need fewer ideas and approaches. As new research is performed and new treatments evolve, this report will expand to include the most accurate, up-to-date information for you and your family members.

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