Diabetes Type II and the Syndrome X Connection

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Approximately 8% of the population in the United States has diabetes. This computes to nearly 16 million people being diagnosed with the disease, based only on national statistics.

The American Diabetes Association announced that diabetes accounts for 178,000 deaths, 54,000 amputees, and 12,000-24,000 cases of blindness annually. Blindness is 25 times more common among diabetic patients compared to nondiabetics. It is proposed that by the year 2010, diabetes will exceed both heart disease and cancer as the leading cause of death through its many complications.

Considering these startling numbers, an insightful internist recently commented that physicians are losing more patients to diabetes than they are diagnosing. Additionally, it is estimated that 5.4 million people have the disease and are not aware of it. Minorities are at particular risk. Compared with Caucasians, blacks have a 60% higher risk of developing diabetes and Hispanics have a 90% increased risk.

Autoimmune (Type I) Diabetes

This type of diabetes has also been called Juvenile Onset Diabetes Mellitus, Insulin Dependent Diabetes, or Type I diabetes. For reasons we do not clearly understand, the body attacks its own insulin-producing tissue, the beta cells of the islets of Langerhans in the pancreas. When so many of these cells are destroyed that not enough are active to meet the body's need for insulin, the patient becomes diabetic and must take insulin injections.

At one time, we thought that this condition was only found in childhood, and so it was assumed that any young person who started showing signs of disturbed glucose metabolism was insulin deficient. Conversely, we concluded that patients who did not become diabetic until they were adults were not insulin deficient. Today, we know that young people can be metabolically diabetic and that adults can become autoimmune diabetic.

Autoimmune diabetes can be definitively diagnosed with blood testing.

Blood insulin and glucose levels, drawn together, will show a deficiency of insulin or an excess of glucose.
Anti-insulin antibodies/anti-islet cell antibodies are usually present in autoimmune diabetes (Type I).

Conventional treatment for this condition is not satisfactory. Replacement of insulin by injection can be used to keep blood sugar under control but will not prevent development of all of the dreaded complications of diabetes: loss of sexual function, diabetic retinopathy (blindness), peripheral neuropathy (approximately 10% of diabetics develop neuropathic symptoms, such as throbbing, aching, or numbness of the lower extremities), and peripheral vascular disease (diminished circulation, intermittent claudication, difficult wound healing, and the propensity for gangrenous body parts and eventual amputation). Typically, tight control of blood glucose levels prolongs the onset and progression of symptoms.

However, there is evidence that protecting cells against the adverse effects of unstable serum insulin and serum glucose can mitigate these complications. Therefore, while many of the supplements in this protocol have documented benefits in protecting against Type II diabetic complications, they can also prevent diseases commonly associated with Type I diabetes.

The Difference Between Type I and Type II Diabetes

Type I diabetes, sometimes referred to as insulin-dependent diabetes mellitus (IDDM), has both similar and dissimilar manifestations as compared to Type II diabetes mellitus. Although both Type I and Type II diabetes often result in similar disabilities, that is, neurological disorders, cardiovascular disease, and sometimes organ failure, the causal factors are quite different. For example, Type I diabetes reflects an inability to

metabolize carbohydrates caused by an absolute insulin deficiency. This type of diabetes occurs most often in children and young adults as a result of inadequate insulin production in the beta cells of the pancreas.

The islets of Langerhans are microscopic structures within the pancreas that are composed of various cell types. The alpha cells secrete glucagon, which accelerates release of stored glucose in the liver (glycogenolysis). The beta cells are most abundant and secrete insulin. The delta cells secrete somatostatin, which regulates release of both glucagon and insulin, among others. (Anatomical Chart Company 2002®, Lippincott Williams & Wilkins)

Type II diabetes generally occurs because of a metabolic failure at the cellular level, a condition spurred by poor diet, obesity, environmental factors, and genetics. Body tissues, such as cell receptor sites, lose their sensitivity. As insulin attempts to deliver glucose into the cell, the "key no longer fits the lock." Blood glucose, barricaded from the cell, accumulates in the bloodstream. Unlike Type I diabetes, insulin therapy is usually not indicated in Type II diabetes because typically these individuals already have too much insulin in their bloodstream. However, after an extended period of excess insulin secretion, the pancreas may lose its ability to produce insulin and a Type II diabetic may then become insulin dependent.

In Type II diabetes, the onset is usually after 40 years of age, but the onset can occur at any age. In fact, the incidence of Type II diabetes among 30-year-olds has gone up over 70% in the last decade. Physicians are increasingly reporting the diagnosis of Type II diabetes in teenagers, as well. The number of teenagers (an age group not normally targeted) being diagnosed with Type II diabetes indicates that a diet structured around high glycemic carbohydrates causes chronic states of hyperinsulinemia. A poorly selected diet, along with a lack of exercise, increases the risk of diabetes and premature cardiovascular disease.

Dr. Alan R. Sinaiko (University of Minnesota) in 2001 announced an association between insulin resistance and an elevation in blood pressure among teenage boys. The teenagers were tested when they were 13 years old and again when they were 15 years of age. By the second test, there was a definite association between the teenage boys' insulin resistance and their blood pressure (Smith 2001). (The reason this did not apply to the girls may be due to the fact that males have a higher overall early risk than females.)

Signs and Symptoms of Diabetes

The symptoms of Type II diabetes can be so subtle that they may be overlooked. But, extreme fatigue (particularly 2-4 hours after a meal), a change in weight, blurred vision, drowsiness, tingling or numbness in hands and feet, slow wound healing, unwarranted hunger (polyphagia), frequent urination (polyuria), and excessive thirst (polydipsia) can be warning signs of abnormal blood glucose levels. Note: Polydipsia and polyuria are homeostatic mechanisms that the body uses to extract sugar from the system.

Diagnostic standards for diabetes have been fasting plasma glucose levels greater than 140 mg/dL on two occasions and plasma glucose greater than 200 mg/dL following a 75-gram glucose load. More recently, the American Diabetes Association lowered the criteria for a diabetes diagnosis to fasting plasma glucose levels equal to or greater than 126 mg/dL. Fasting plasma levels outside the normal boundaries require additional testing, usually by repeating the fasting plasma glucose test and (if indicated) undergoing an oral glucose tolerance test.

Glucosuria (sugar in the urine) usually occurs when blood glucose levels reach 160-180 mg per 100 mL of blood. However, this does not confirm diabetes because a nondiabetic can have a normally low renal threshold (Krause et al. 1984).

Diabetic patients often have skin tags, that is, pouches of skin that tend to grow on the neck and in the armpit and groin regions (Kahana et al. 1987). Researchers studied 35 men and women with skin tags (average age of 52 years). The association between skin tags and diabetes appeared in 62.8% (22 patients) (Thappa 1995). A similar study concluded with like findings. After evaluating a small group of subjects in regard to the significance of skin tags, the researchers concluded that skin tags

appear to be a useful clinical assessment in identifying individuals at high risk for coronary artery disease, hypertriglyceridemia, decreased HDL, impaired glucose tolerance, and Type II diabetes (Crook 2000). Note: The frequency with which skin tags coexist with diabetes mellitus, rather than the localization, size, color, or number, indicates that clinicians should note skin tags in physical examinations (Thappa 1995).

Secondary diabetes is a condition with a different pathogenesis (source or cause) than either Type I or Type II diabetes. In secondary diabetes, a primary condition, such as chronic or recurrent pancreatitis (an inflammatory condition of the pancreas), can result in diabetes. Also, adverse responses to medications can bring on secondary diabetes. For example, Skarfors et al. (1991) announced that certain drugs prescribed to treat hypertension (beta blocking agents, thiazides, or hydralazine) decreased insulin sensitivity. According to information released from Oregon Health Sciences University (Portland), antipsychotic medications (clozapine, olanzapine, or quetiapine) increased the occurrence of diabetes (Muench et al. 2001). Navajo women receiving Depo-Provera (medroxyprogesterone, an injectable contraceptive) also had a greater incidence of diabetes, compared to those receiving oral estrogen and progestin combinations (Kim et al. 2001).

About 2-5% of all pregnancies induce gestational diabetes, but it is usually a transient condition that terminates postpartum. However, the risk of developing diabetes in later years is greater for both mother and infant.

The focus of this protocol is on Type II diabetes, the type that affects 90-95% of the diabetic population, defining contributing factors and detailing a comprehensive program to render the condition (if not reversible) highly manageable. If you are a Type I diabetic, many of the therapeutic recommendations contained in this protocol can reduce the incidence of common diabetic complications.

Note: Type II diabetes is sometimes referred to as noninsulin dependent diabetes or adult-onset diabetes. These terms are being discontinued because some Type II diabetics go untreated so long that they become dependent on insulin injections; in addition, there are very young people developing Type II diabetes primarily from poor diet and lack of exercise.

ARE SYNDROME X AND TYPE II DIABETES THE SAME CONDITION?

Dr. Gerald Reaven, M.D., an authority on insulin resistance and hyperinsulinemia, coined the term Syndrome X (in 1988) to identify clusters of symptoms that often accompany abnormal blood glucose levels: hyperlipidemia (too much cholesterol and triglycerides in the blood), hyperinsulinemia (too much insulin in the bloodstream), obesity, and hypertension. Syndrome X, like Type II diabetes, is a condition of insulin resistance, a disorder in which insulin does not produce the same glucose-lowering effects seen in otherwise normal, insulin-sensitive individuals. The failure occurs at the cellular level, robbing insulin of its primary role of glucose delivery.

Syndrome X and many cases of early stage Type II diabetes are conditions of insulin resistance and excesses of compensatory insulin. Hyperinsulinemia, in most cases is only a temporary reprieve in delaying the onset of full-blown diabetes. The pancreas will eventually become weary in its effort to supply the extra insulin needed to forestall the disease.

It is important to note that while almost all Type II diabetic patients are insulin resistant, not all individuals with hyperinsulinemia become diabetics. Although opinions are varied as to the numbers, some speculate that one in four hyperinsulinemic individuals will become diabetics (Lukaczer 1999). Should the individual escape diabetes, hyperinsulinemia is still a significant risk to long-term survival. Note: Several decades ago, investigators at the Bronx Veterans Administration Hospital showed that patients with Type II diabetes could have elevated blood glucose levels despite having higher insulin levels, a revelation that stunned the medical community.

Diagnosis of Syndrome X

- Bad Genes

There are clusters of symptoms that make up a syndrome, and the symptoms common to Syndrome X deserve close monitoring. For example, men with a previous history of recurrent calcium oxalate kidney stones may have elevated insulin levels (Schwille et al. 1997). Women with a history of hirsutism (excessive body hair), oligomenorrhea (scanty periods), infertility, or polycystic ovary disease often have an underlying hyperinsulinemic condition (Nestler et al. 1991, 1996, 2002).

Part of the Syndrome X profile includes an earlobe crease appearing at a 45-degree downward angle toward the shoulder and an elevated waist to hip circumference. Bouts with low blood sugar, carbohydrate intolerance, sugar cravings, sleepiness after meals, insomnia (relieved by snacking), adult acne, and central abdominal obesity are signs suggestive of insulin excess. The patient may present with elevated serum uric acid and ferritin levels, moderately elevated blood pressure, and an abnormal lipid profile. While these factors are commonly observed in the hyperinsulinemic adult, longitudinal studies suggest that elevated insulin levels may start in childhood, particularly in the overweight youngster displaying abnormal blood lipids (Bernard et al. 1992; Lukaczer 1999; Goran 2001).

Triglycerides and HDL cholesterol are significantly impacted by hyperinsulinemia (triglyceride levels are typically elevated and HDL levels are depressed). Insulin actually has very little effect quantitatively on total cholesterol or LDL cholesterol levels (Bland 2000). It is speculated that either the elevated triglycerides or the insulin resistance and the resulting excess of insulin may, however, cause the LDL cholesterol particles to assume a smaller, denser configuration, a hallmark of Syndrome X. Studies have shown an association between the highly atherogenic, smaller diameter LDL particles and insulin resistance (Reaven 2000).

The decrease in the "good" cholesterol (HDL) also impacts the ratio between LDL and HDL cholesterol (a high LDL-to HDL ratio is another risk factor associated with cardiovascular disease). Persons with Syndrome X often present with HDL levels less than one-fourth of the total cholesterol, a burdening handicap to cardiac health (Challem, 2000).

Although normal fasting glucose does not directly indicate the degree of insulin resistance, impaired glucose tolerance (fasting glucose 111 to125 mg/dL) and frank diabetes (fasting glucose greater than 125 mg/dL) is a useful prognosticator. According to the Functional Medicine Research Center (Gig Harbor, WA), the best practical measure of insulin resistance and hyperinsulinemia may be fasting and two-hour postprandial serum insulin values following a 75-gram glucose challenge. Elevations above 15 mcIU/mL (fasting) and/or 50 mcIU/mL (postprandial) signify increased insulin secretion secondary to insulin resistance (Bland 2000).

Comment: It is important to note that laboratory values reflecting optimal health may be considerably lower than values used to denote Syndrome X. For example, the Life Extension Foundation believes that fasting insulin levels above 5 mcIU/mL may be a cause for concern and many respected physician/scientists are aligning with this projection.

Blood pressure may be chronically elevated, that is, consistently above 140/90 mmHg in Syndrome X patients. As few as 10 pounds of excessive weight can also indicate problems, particularly when the extra pounds are also associated with elevated blood fats and hypertension (Challem et al. 2000).

A physician will also perform liver function tests (gamma-glutamyltransferase) and evaluate the adequacy of magnesium, which is often depressed in insulin-resistant/hyperinsulinemic individuals. (Rosolova et al. 1997; Perry et al. 1998). In men, low levels of free testosterone also correlate with Syndrome X.

Clinically, the spectrum of patients with some degree of insulin resistance falls into four overlapping categories. The first category includes the individuals with a mild degree of insulin resistance (as measured by one or more of the above-mentioned criteria). Borderline laboratory values (coupled with physical exam and positive

family history) may prompt the clinician to initiate diet and lifestyle changes. The second category includes the individual who clearly shows signs and symptoms of insulin resistance: central abdominal obesity, increased triglycerides, depressed HDL, elevated fasting insulin with normal glucose, and an often startling elevation in two-hour postprandial plasma insulin. This is the classic Syndrome X insulin-resistant picture with a marked compensatory hyperinsulinemia (Bland 2000).

The last two categories include the remaining insulin-resistant patients, that is, those with either impaired glucose tolerance or overt diabetes. Although these individuals are almost always insulin-resistant, they are no longer able to compensate adequately by secreting large amounts of insulin to normalize serum glucose levels. In these cases, fasting and two-hour insulin measurements are of key importance.

The third category includes the patient who is able to mount an insulin response on glucose challenge and is therefore hyperinsulinemic. This patient appears more physiologically capable of normalizing serum glucose through diet, supplementation, and other lifestyle interventions.

In the fourth category, the patient with little response to challenge is insulin-resistant as well but has apparently lost significant ability to secrete insulin. Improving insulin sensitivity continues to be of critical importance; however, additional medications to either exogenously supply or to endogenously stimulate insulin may also be necessary (Bland 2000).

Is Syndrome X Caused by Bad Genes?

If your family history includes heart attacks, hypertension, and Type II diabetes, the likelihood of being insulin resistant increases. It appears about 50% of the variability of insulin may be due to genetic propensities; the other half seems related to lifestyle. According to Dr. Gerald Reaven, author and authority on Syndrome X, of the 50% attributed to lifestyle, half may be due to a lack of fitness and half to obesity (Bogardus et al. 1985; Reaven 2000). Some researchers speculate that the genetic link may also be strongly influenced by mimicry. Offspring may (in fact) be mimicking the poor eating habits of parents, producing another generation plagued by obesity, insulin insensitivity, and diabetes.

Jeff Bland, Ph.D. (Functional Medicine Update, June 2001), explains that hyperinsulinemia is a polygene inheritance across multiple genes, not just a single gene. Research in human genetics indicates that impaired beta cell function, increased hepatic glucose production, and decreased insulin peripheral sensitivity appear to be genetic disorders exacerbated by environmental factors. According to Bland, "Environment is modifiable; genes are not."

WHAT CAUSES INSULIN RESISTANCE AND WHAT ARE THE EFFECTS?

Until recently, one of the most popular explanations regarding insulin resistance was that some individuals are born with bad cellular receptors, which ultimately require the overproduction of compensatory insulin. According to information in The Institute of Nutritional Science Journal (Whiting 2000), diabetic patients may be born with a genetic fault that causes their bodies to overproduce insulin when sugar or sugar-forming foods are consumed. As excesses of insulin wash over the delicate insulin-receptors located on cell membranes, the powerful hormone robs more and more of the receptors' sensitivity. If the insulin saturation becomes too extreme, the receptors can be totally burned out. Reckless carbohydrate consumption exacerbates this sequence.

During insulin resistance, the pancreas is aware of the hyperglycemia (mounting glucose in the bloodstream) and, in an effort to correct the malfunction, discharges copious amounts of insulin as a compensatory gesture. Although this homeostatic mechanism allows glucose to enter the cell, hyperinsulinemia results. Unfortunately, a number of drugs prescribed to treat Type II diabetes stimulate the pancreas to produce more and more insulin. This approach temporarily lowers blood glucose levels but at the expense of the insulin receptor. Although debated, some contend that a surplus of insulin in the bloodstream causes more medical complications than an excess of glucose.

It is important to note that the cell is surrounded by a plasma membrane composed of a double layer of phospholipids. This double layer of lipids provides

a site of dissolution for molecules that are soluble in lipids. Protein molecules float in the phospholipids, adding structural support, membrane channels, carrier molecules, enzymes, and receptor molecules. The binding of insulin to its receptor in the cell membrane is the first step in a metabolic cascade that results in a glucose uptake in insulin-sensitive tissue.

Historically, the cell membrane has been regarded as the most dynamic feature of the cell. It has become increasingly clear that alterations in membrane lipid composition and membrane fluidity influence pivotal cellular functions such as the transport of substances across the cell membrane and the activity of receptors (Adamo et al. 1988). By contributing to the sluggish transport and irresponsiveness of the receptor, altered membrane activity can be an important factor leading to Type II diabetes. Nutritional imbalances that might be affecting the integrity of the cell membrane should be a principal focus of treatments targeted at hyperinsulinemia (Kinnunen et al. 1991).

So which one of the explanations regarding damage occurring at the insulin receptor is most reliable? Does the lack of receptor sensitivity occur because of an unstable plasma membrane, a genetic disadvantage, or abusive consumption of carbohydrates? In truth, any one of the premises or a combination thereof can damage the receptor's responsiveness. A positive finding is that the insulin receptor is resilient. When insulin concentrations in the bloodstream are reduced, the receptor may be able to reestablish sensitivity, resulting in better blood sugar control with only a fraction of the insulin previously required.

What are the Risks Imposed by Hyper- and Hypoglycemia?

- Low Blood Glucose Levels

Diabetes independently imposes such stress upon the heart and vascular system that the diabetic frequently succumbs from a cardiovascular event rather than the disease itself. In the Cardiovascular protocol in this book (Diabetes and Syndrome X sections), diabetes-induced damage to the heart and blood vessels (the major complication arising from abnormal blood glucose levels) is thoroughly described and will not be repeated in this protocol. The reader is strongly advised to read those sections for valuable information regarding the role unstable blood glucose plays in heart and vascular disease.

Most healthy individuals maintain postabsorptive blood glucose levels of 90-100 mg/dL. Even after fasting or overeating, blood glucose levels seldom fluctuate lower than 60 or over 160 mg/dL. Unstable diabetics lack the homeostatic control to maintain blood glucose within a normal range; subsequently, blood glucose levels can oscillate from hyperglycemia to hypoglycemia within a few hours.

The effects of too much or too little blood glucose or insulin in the bloodstream are usually as diverse as they are serious. For example, chronic hyperinsulinemia causes tissues to receive insulin that do not require it. Renal glomeruli (kidney structure composed of blood vessels or nerve fibers), ocular lens, and peripheral nerves are among those tissues most damaged. Kidney disease (17 times more frequent among diabetic patients), cardiovascular disease, gangrene, retinopathy, and damage to the nervous system are relatively common in chronically unstable diabetic patients. Another grim finding is that hyperglycemia impairs the activity of nitric oxide, resulting in endothelial dysfunction. This, in turn, causes vasoconstriction, smooth muscle proliferation, platelet activation/aggregation, and leukocyte adherence to the endothelium (Adrie 1996; Cooke et al. 1997; Federici et al. 2002).

Hyperglycemia and excesses of ineffective insulin cause rampant free-radical activity, lipid peroxidation, glycation (the pathological union of protein and sugar), and increased inflammation (Sears 1999). Impotence, depression, cataracts, glaucoma, atherosclerosis, and dementia often negatively impact a diabetic's quality of life. Subjects with Type II diabetes have a 1.9 relative risk of both dementia and Alzheimer's disease and that risk jumps to 4.3 among patients receiving insulin (Ott et al. 1999). It is hypothesized that vascular disease or the nonvascular effects of diabetes could explain the increased risk of dementia. It was also pointed out that both hyperglycemia and hypoglycemia are thought to have adverse effects on the brain. (Relative risk

denotes the chance of a disease developing among members of a population exposed to a factor compared to a similar population not exposed to the factor.)

The degree and duration of hyperglycemia appear to dictate the frequency and pathological intensity of complications arising from diabetes. People with Type II diabetes generally are not prone to ketosis and acidosis, but extremely high blood glucose levels pose another significant endangerment: a coma, usually the result of dehydration, which if left untreated is fatal about 50% of the time. (This type of coma is termed hyperosmolar, hyperglycemic, nonketotic coma.) Troublesome physical events quickly mount against an uncontrolled diabetic, shortening life expectancy by about one-third compared to the nondiabetic population.

Blood Glucose/Insulin Equation

High blood glucose/high insulin levels
=
accelerated aging and an increased risk of premature death

An unstable diabetic faces additional challenges if blood glucose levels become too low (hypoglycemia). For example, normal brain function requires 6 mg of glucose an hour, which can only be delivered if arterial blood contains over 50 mg/dL of glucose. Dizziness and blurred vision are symptoms of hypoglycemia, but if blood glucose levels truly plummet, unconsciousness can result. (Extremes at either end of the glycemic scale can result in loss of consciousness.)

Factors that Provoke Low Blood Glucose Levels

- Dietary carelessness (excesses of refined carbohydrates or foods high on the glycemic index) can cause hypoglycemia. Sugary treats can cause blood glucose levels to rocket, followed by a rapid fall. (See the section in this protocol devoted to the Glycemic Index for a more in-depth look at insulin-provoking foods.)
- Stress-induced hypoglycemia occurs when frustration and arousal command the adrenal glands to release cortisol and adrenaline. Increased hormonal activity causes a precipitous rise in blood sugar, followed by an abrupt plunge. Hypoglycemic individuals often report varying degrees of panic and terror, a response likely orchestrated by the action of adrenaline. Overwhelming fatigue results as the body absorbs the stress of the glucose seesaw.
- Using insulin when insulin is not indicated, too much insulin even when insulin is justified, or oral insulin-inducing diabetic medications can produce the same blood glucose swings.

GLUCOSE, INSULIN, AND GLUCAGON

- Insulin-Liver Connection

Major control of blood glucose levels is achieved through actions of the hormones insulin and glucagon. The slightest rise in plasma glucose leads to a decrease in glucagon secretion and an increase in insulin secretion. The reverse occurs when plasma glucose levels fall. A network of interrelated responses from the liver, pancreas, pituitary, adrenal, and thyroid glands joins forces to ensure that the rate of glucose entry into the blood is balanced by its rate of withdrawal (Pike et al. 1984).

The pancreas, detecting excess glucose in the bloodstream, takes immediate steps to counter the glucose rise by supplying the hormone insulin. Insulin, in turn, is responsible for marshaling glucose to the receptor site for cellular entry. Stimulating glucose transport into muscle and adipose tissue is a crucial component of the physiologic response to insulin. However, the pancreas demonstrates its diversity by also supplying the hormone glucagon (produced from the alpha cells in the islets of Langerhans). Glucagon has the opposite effect of insulin. Glucagon summons the release of glycogen (the stored form of glucose) from the liver to form glucose when blood sugar levels become too low, a process referred to as glycogenolysis (the breaking down of glycogen). The secretion of glucagon is stimulated by a state of hypoglycemia and the growth hormone from the anterior pituitary gland.

Glycogen (glucose stored in the liver) is a major force in glucose control, but it is the liver (receiving instructions from hormones and neural stimuli) that holds dominion over glycogen pathways. By both

supplying glucose when blood levels are low and accepting glucose when blood levels are high, the hepatocytes (liver cells) become key participants in glucose/glycogen homeostatic mechanisms. It should be noted that the muscles stockpile about two-thirds of glycogen but use most of this supply to provide for their own energy requirements. The liver stores the remaining one-third, releasing it when blood levels of glucose are no longer adequate to meet metabolic demand (Hamilton 1988). Normally, an adult will have about three-fourths of a pound of glycogen (340 grams) stored in the liver and muscles at one time (Krause et al. 1984).

The Insulin-Liver Connection

Internal checks and balances, warranting safe blood glucose levels, are as vital as they are amazing. A status favoring neither hyper- nor hypoglycemia occurs through the interaction of hormonal and neural stimuli, as illustrated by the following examples:

- Insulin's primary action in the hepatic (liver) cell is the inhibition of glucagon-mediated activity by
  - Blocking glycogenolysis (the degrading of glycogen to form glucose) as well as inhibiting gluconeogeneis (the formation of glucose from noncarbohydrate sources, such as lactate, pyruvate, glycerol, and certain amino acids) (Pike et al. 1984).
  - Removing the glucagon block on liver glycogen synthase. An increased conversion of glycogen synthase to its active form explains a part of the known effect of insulin on glucose uptake by the liver cell (Villar-Palasi et al. 1971; Pike et al. 1984).

- Another action of insulin is induction of the activity of glucokinase, increasing the uptake of glucose by the liver when plasma glucose levels are elevated (Czech 1980). The Therapeutic Section of this protocol describes how biotin works synergistically with insulin to increase the activity of glucokinase, an enzyme responsible for the first step in glucose utilization (Murray 1996). Glucokinase, with the help of ATP, catalyzes glucose to glucose 6-phosphate, an intermediate in carbohydrate metabolism.

Epinephrine, an adrenal medulla hormone, and thyroxin, a hormone secreted by the thyroid gland, also stimulate glycogenolysis, the breakdown of glycogen to supply a ready source of glucose. Glucocorticoids, particularly cortisol, tend to increase glucose production by the liver cells and decrease glucose utilization in both muscle and fat cells. These actions are inclined to counteract the effects of insulin and subsequently increase blood glucose concentrations.

Comment: In a postabsorptive state, blood glucose concentrations are ideally maintained within a normal range of 80-100 mg/dL by glycogenolysis (the formation of glucose from glycogen) and gluconeogeneis (the formation of glucose from noncarbohydrate sources). Since liver glycogen capacity is rather limited, the ability of liver cells to tap more extensive sources of ultimate glucose (gluconeogenesis) is keenly important. Both mechanisms, glycogenolysis and gluconeogenesis, occur within the liver cell, but under certain circumstances such as starvation, the kidney is equally important in providing glucose from noncarbohydrate sources. In a healthy individual (even during periods of fasting or overeating) blood glucose levels remain remarkably constant because of the efficiency and rapidity of these systems (Unger 1981). It should be noted that the most vital function of glucagon is to maintain plasma glucose at a level adequate for the function of the central nervous system regardless of energy intake or energy expenditure.

Maintaining a healthy liver (capable of fully participating in blood glucose control) is vital. Please consult the Therapeutic Section of this protocol to read about silymarin, a liver protector and hypoglycemic agent.

GUM DISEASE IN DIABETES

The importance of gum health is confirmed in heart disease, but according to data released from the University at Buffalo (UB) School of Dental Medicine, diabetes can be added to the growing list of systemic diseases and conditions associated with bacteria from infected gums (Baker 1999a). Research has emerged suggesting that the relationship between periodontal disease and diabetes goes both ways, that is, periodontal disease

may make it more difficult for people who have diabetes to control their blood sugar and poorly controlled Type II diabetic patients are more likely to develop gum disease.

Researchers from UB studied 11,198 nondiabetic subjects (ages 20-90) from the Third National Health and Nutrition Examination Survey (NHANES III) conducted from 1988 to 1994 for their evaluation. They assessed the degree of gum detachment from bone, along with fasting-insulin and fasting-glucose levels.

Gram-negative periodontal infections were found to be significantly associated with insulin resistance. Gram-negative bacteria appear to produce a very potent toxin called LPS, which probably interferes with the action of insulin and is responsible for maintaining a chronic state of insulin resistance in individuals with gum infections (Baker 1999a).

As insulin resistance increases, the severity of periodontal disease also increases. Results show that those with severe gum detachment (regardless of weight, smoking status, gender, or age) have a higher index of insulin resistance than those with little or no gum disease.

Note: Researchers used a body mass index (BMI) of 27 as the dividing line between acceptable and unacceptable degrees of obesity (Baker 1999a). See the chart relating to BMI in the section How Is Obesity Linked to Hyperinsulinemia and Diabetes?

Another study conducted at the University of Buffalo (involving 168 adults with diabetes) showed that those with severe gum deterioration had the most difficulty controlling blood glucose levels (Millman 2001). Some explain that oral bacteria, fed and nurtured by excesses of sugar, escape from the gums and enter the bloodstream. This summons the immune system into action, and cytokines (proteins that amplify immune reactivity) enter the milieu. In an attempt to kill out the bacteria, cytokines overstep their role and attack pancreatic cells, as well (Reuters Health 2001). An assault on the beta cells compromises their ability to supply insulin, and glucose builds up in the bloodstream. This sequence provides more sugar, perpetuating a classic, vicious cycle.

Note: Poorly controlled diabetics also have more cytokines in the gingival tissue, causing destructive inflammation of the gums. In turn, growth factors are also reduced, interfering with the healing response to infection (Cutler et al. 1999; Strayhorn et al. 1999; AAP 2002)..

In 1997, 113 Pima Indians (having both diabetes and periodontal disease) were treated for their gum conditions. The participants (81 females and 21 males) were divided into 5 groups. All underwent ultrasonic scaling and curettage combined with an antimicrobial regime that consisted of (1) topical water and systemic doxycycline, 100 mg for 2 weeks; (2) topical 0.12% chlorhexidine (CHX) and systemic doxycycline, 100 mg for 2 weeks; (3) topical povidone-iodine and systemic doxycycline, 100 mg for 2 weeks; (4) topical 0.12% CHX and placebo; and (5) topical water and a placebo.

Clinical assessments by probing depth, clinical attachment level, the detection of Porphyromonas gingivalis in subgingival plaque, and the determination of serum glucose and glycated hemoglobin (HbA1c) were performed prior to and at 3 months and 6 months after treatment. All study groups showed clinical and microbial improvement, but the doxycycline-treated groups showed the greatest reduction in probing depth and P. gingivalis infection. All three groups receiving systemic doxycycline showed (at 3 months) significant reductions in mean HbA1c--reaching nearly 10% from the pretreatment value (Grossi 1997).

The control of periodontal infections is essential as a prophylactic against diabetes, as well as for better blood glucose control among confirmed diabetics. If neither a medical nor dental provider has explored the gum disease-diabetes association, a patient should consult a periodontist for an assessment regarding the health of the gums.

Note: A study presented at the International Association for Dental Research concluded that overweight people with the highest levels of insulin resistance were about twice as likely to have severe periodontal disease, compared to overweight people with low insulin resistance. Researchers speculate that bacteria from gum disease may be interfering with fat metabolism, promoting both obesity and hyperlipidemia. The obesity-periodontal disease

relationship is particularly significant because both are major factors in Type II diabetes.

HOW IS OBESITY LINKED TO HYPERINSULINEMIA AND DIABETES?

- Carbohydrate Digestion and Absorption
- Macronutrients
- Fats
- Gylcemic Index and Dietary Recommendation
- Exercise
- Stress

The Centers for Disease Control and Prevention reported that extra pounds and inactivity are to blame for hundreds of thousands of premature deaths in the United States annually. As girth increases, the chance of developing some form of ill health dramatically increases, including the risk for diabetes. At least 10 million overweight Americans could sharply cut their risk of developing diabetes by making relatively simple lifestyle changes, e.g., altering eating habits (restricting calories to 1200-1800 a day) and introducing exercise into their daily regime. Walking should never be discredited as a viable form of exercise; as little as 30 minutes of walking a day can dramatically improve the plight of prediabetic and diabetic patients (Cafazzo 2001; Blake 2002). (Read the section entitled Exercise: Helpful in Blood Glucose Control in this protocol.)

The Diabetes Prevention Program (a 3-year study) was the first large-scale study to show that losing weight and exercising can effectively delay diabetes. A study reported in the New England Journal of Medicine, involving 84,041 nondiabetic female nurses tracked from 1980-1996, substantiated earlier findings. During the 16-year follow-up, 3300 new cases of Type II diabetes were documented. Obesity was the single most important predictor of diabetes, but a lack of exercise, poor diet, and current smoking also contributed to the risk. The researchers concluded that the vast majority of cases of Type II diabetes (about 90%) could be prevented by the adoption of a healthier lifestyle (Hu et al. 2001).

It appears not to be a fluke that 50-90% of all people with Type II diabetes are overweight. According to Dan Lukaczer, N.D., obesity and chronic hyperinsulinemia induce insulin resistance in peripheral tissues. Chronic hyperinsulinemia (in turn) is a predictor of obesity. The Tulane National Center for Cardiovascular Health has determined that individuals with consistently elevated insulin levels (versus those with normal insulin levels) had a 36-fold increase in the prevalence of obesity (Bao et al. 1996). Many hormones play a role in fat regulation, among them cortisol, estrogen, androgen, and insulin, but hyperinsulinemia makes weight management particularly difficult.

Hyperglycemia is also involved in obesity. If the body takes in more carbohydrates than needed (glycogen stores are filled and energy requirements are satisfied), the leftovers are broken down (by the liver) to smaller fat molecules. The fat then travels to fatty tissues of the body where it takes up residency. Unlike the liver (which has limited glycogen capacity), fat cells can store unlimited quantities of fat (Whitney 1998). Researchers (addressing the conversion of glucose to fat) make the challenge that one has to be "prepared to play the game" if excessive amounts of carbohydrates are consumed (Hamilton et al. 1988).

Although obesity often parallels Type II diabetes (about 90% of newly diagnosed Type II diabetic patients are overweight), many obese patients do not display insulin resistance, and about 50% of hyperinsulinemic patients (those not yet diagnosed with diabetes) are of normal weight (Bogardus et al. 1985; Zavaroni et al. 1994).

BMI appears to be a valuable tool in assessing the gravity of obesity as a contributor to Type II diabetes. BMI may be calculated as follows:

- Determine body weight in pounds and convert to kilograms (1 kg = 2.2 pounds).
- Determine height and convert to inches.
- Convert height in inches to meters. Divide height in inches by 39.37 (1 meter = 39.37 inches).
- Square height in meters by multiplying it by itself.
- Divide weight in kilograms by height in meters squared.

Men	Women
BMI >35 = 42-fold increase in diabetes	BMI of 25 = 5-fold increase in diabetes
	BMI of 30 = 28-fold increase in diabetes
	BMI >35 = 93-fold increase in diabetes

As problematic as a few extra pounds are in Type II diabetes, a weight loss can be just as significant. When Type II diabetic patients lost from 1.5-14% of their body weight, all diabetic parameters improved, that is, fasting blood glucose, hemoglobin A1c, plasma insulin, triglycerides, and HDL cholesterol. Those who lost 15% of their body weight were able to discontinue oral diabetic therapy. According to Priscilla Hollander, M.D., consuming 100 extra calories a day can result in a weight gain of approximately 12 pounds over 1 year; the consequence of consuming 200 extra calories a day reflects a 24-pound annual gain.

Certain factors remain constant: a weight loss increases insulin sensitivity and deters the onset and progression of diabetes. Also, when blood insulin levels are reduced, the patient experiences an almost automatic weight loss. If the reader needs help with weight management, please consult the Obesity protocol for direction on suppressing excess insulin levels.

Simple and Complex Carbohydrates: Their Digestion and Absorption

Carbohydrates are probably the largest group of foodstuffs most individuals consume with regularity. It is estimated that 60-90% of the average American diet is composed of carbohydrates, ranging from simple sugars and fast foods to grains and starchy vegetables, such as potatoes, corn, and beans.

The least complex of all carbohydrates are the simple sugars (monosaccharides), which require virtually no digestion to metabolize. This means that after consumption they swiftly flood the bloodstream. If these food factors are eaten, it must be with extreme caution to avoid crowding the bloodstream with unnecessary burdens of glucose and insulin (Whiting 1989).

Glucose, a monosaccharide also known as dextrose, is the only sugar that can be utilized by the body. All other forms of starches and sugars must eventually be broken down and converted to glucose. Fructose or levulose (also a monosaccharide) is found in fruits and honey. The concept that fructose, in a concentrated form, is a better choice for the diabetic is erroneous; the release of fructose into the system takes only slightly longer than glucose. Fiber and attending enzymes in fruits assist in metabolizing the sugar, making naturally occurring fructose far less problematic than isolated concentrations. Unfortunately, fruits are not all equally safe for individuals with unstable blood glucose levels. Please consult the Glycemic Index (in this protocol) to read about fruits that are less likely to prompt a rise in blood sugar and an insulin rush.

The more complex sugars in the soluble group are made of double bonds (disaccharides) that are broken down by specialized enzymes within the body. Sucrose, common table sugar (a disaccharide), is one of the sweetest and perhaps the most tempting of all sugars. In order for sucrose to be absorbed, it must be broken down into two simple sugars, such as fructose and glucose. Lactose, also known as milk sugar, is the least sweet of sugars from the disaccharide group because it is less soluble.

The starch group of foods is regarded as insoluble. Starches are classified as insoluble because of the complex process required in breaking down complex starches into disaccharides and eventually to basic sugars or monosaccharides. Of all the carbohydrate groups, polysaccharides (complex carbohydrates) are probably the most beneficial to human metabolism. Types of polysaccharides (often extremely complex with long chains of glucose molecules) are cellulose (the primary constituent of plant cell walls), hemicellulose (the main constituent of cereal fibers), pectin (found in vegetables and fruits), and gums and mucilages (plant secretions). Examples of food sources include wheat, oat bran, and stalks and leaves of vegetables, seeds, and fruits. Raw, unrefined, or unprocessed

carbohydrates are surrounded with other valuable food factors, such as protein, fats, vitamins, and minerals.

The time required to break down a complex carbohydrate minimizes the risk of overloading the body with a blast of sugar and a sudden release of insulin from the pancreas. A complex carbohydrate may, in fact, take hours to convert to glucose, rather than the few minutes required for processing a simple sugar.

- Note: While complex carbohydrates usually serve diabetic individuals far better than simple sugars, some individuals find carbohydrates (in general) problematic. This likely occurs because of food allergies or exaggerated consumption of carbohydrates in relationship to other macronutrients (fats and protein). Consult the following section to learn the percentage of carbohydrates, proteins, and fats deemed most desirable in a diet to control blood glucose levels and symptoms of Syndrome X.

The Biochemical Nature of Macronutrients (Carbohydrates, Fats, and Protein)
Foods, that is, macronutrients, deliver powerful messages. According to Barry Sears, Ph.D., "Once food is broken down into its basic components (glucose, amino acids, and fatty acids) and sent into the bloodstream, it has a more powerful impact on your body and your health than any drug your doctor could ever prescribe."

The principal function of carbohydrates is to serve as a major source of energy for the body. If insufficient carbohydrates are available, the body will convert protein to glucose in order to supply energy (gluconeogenesis). The energy needs of the body take precedence over all other requirements (Krause et al. 1984). But, if consumed in excess, carbohydrates overwork the pancreas and are an invitation to obesity, diabetes, hypertension, hyperlipidemia, and some types of arrhythmias.

Proteins are the main structural components of cells and the enzymes that keep the cells running. Even our immune systems are essentially composed of protein (Sears 1995). However, proteins, when consumed in excess, create demands for vitamin B6 and calcium, stress the kidneys, and promote a weight gain. There are, however, several opinions regarding the influence protein has on insulin levels:

- According to various researchers, protein blunts a glucose rise and insulin response in normal glucose-tolerant individuals (Wang et al. 1991; Garg et al. 1994).
- Proteins primarily stimulate glucagon (a hormone that releases stored carbohydrates in the form of glucose from the liver); if too much protein is taken in at a meal, insulin levels will increase (Sears 1995).
- Dr. Gerald Reaven (head of endocrinology, gerontology, and metabolism at Stanford University) challenges: "Why trade one insulin-raising nutrient for another? It is far safer, and just as nutritious, to decrease carbohydrates and maintain protein at a reasonable level, while increasing your intake of the `good' unsaturated fats" (Reaven et al. 2000).
- According to information in the American Journal of Clinical Nutrition, protein induces an increase in insulin concentrations when ingested in combination with carbohydrate. A mixture of wheat protein hydrolysate, free leucine, phenylalanine, and carbohydrate can be applied as a nutritional supplement to strongly elevate insulin concentrations (van Loon 2000).

Poorly selected fats produce a harvest of undesirable (even destructive) hormone-like substances such as PGE2, a prostaglandin produced from arachidonic acid. It appears, however, that fats (saturated or unsaturated) neither increase nor decrease insulin levels. It is only when fats replace carbohydrates that insulin levels drop and the clusters of symptoms associated with Syndrome X become less apparent (Reaven 2000).

While opinions differ on the amounts of macronutrients one can safely ingest at a meal, it is safe to say that carbohydrate begets insulin. In other words, the more carbohydrate consumed, the more insulin is secreted. The epidemic proportions of diabetes indicate many Americans are asking their body to run on fuel not recommended. Illustrative of the dietary transgressions our society has committed, in the early 1800s the per capita

consumption of sugar (sucrose) was about 12 pounds a year. Today in the United States, the per capita consumption of sugar is more than 150 pounds a year. For every person who consumes only 5 pounds of sugar, there is another who eats 295 pounds annually (Challem et al. 2000).

According to Dr. Reaven, drawing 45% of calories from carbohydrate, 40% from "good" fats, and 15% from protein benefits individuals with Syndrome X. Nutritionists, reviewing the concept of macronutrient fractions, stress the importance of selecting healthy foods to supply requirements; eating ad libitum from unwise food choices (but within acceptable percentages) could still render the diet unhealthy from many perspectives.

The standard diabetic diet, currently recommended by most physicians, is very high in carbohydrates, about 65% of calories supplied by starches. This diet increases blood sugar, stimulates insulin production, and reduces the sensitivity of the insulin receptor. Steven Whiting, Ph.D., says that chronic adherence to a high carbohydrate diet ensures that the diabetic individual will be a patient for life, never recovering but slowly worsening in a downward spiral of ever-increasing side effects.

Good Fats

The current dietary trend away from fats and toward carbohydrates can be a fatal departure for an individual with Syndrome X and Type II diabetes. We have been led to believe that fats do little more than make us fat. A partial list of functions assigned to dietary fat discredits this logic:

- Fats slow the secretion of hydrochloric acid, prolonging the digestive process. Fats, therefore, provide more sustained satisfaction after meals and the desire to eat is delayed.
- Fats regulate the production of prostaglandins (hormone-like messengers).
- Fats serve as carriers for the fat-soluble vitamins such as vitamins A, D, E, and K. By aiding vitamin D absorption, fats keep calcium readily available to bones and teeth.
- Fats (omega-3 fatty acids) increase insulin sensitivity.
- Fats are mood enhancers, reducing levels of antagonism, rage, and despair. (Negative emotions transcend to impaired physical responses.)

According to data in the American Journal of Clinical Nutrition, trans fatty acids (often appearing in cookies, cakes, and processed foods) dramatically increase a woman's risk of developing diabetes. A trans fat (a fatty acid that the body is not able to successfully metabolize) results when a cis fat is exposed to hydrogenation, overheating, or refining.

Researchers (in the preceding study) followed the medical and dietary histories of 84,204 nondiabetic women over 14 years. From this group, 2507 cases of Type II diabetes were documented. Statistics showed that intake of total fat, saturated fat, and monounsaturated fat (as found in nuts, seeds and avocados), did not influence diabetic risk. However, a 2% increase in calories from trans fatty acids raised the risk by 39%, and a 5% increase in calories from polyunsaturated fat reduced the risk by 37%. It is speculated that substituting foods rich in trans fats with polyunsaturated fats could reduce the risk of Type II diabetes by nearly 40% (Salmeron et al. 2001).

Dietary choices of fats, generally regarded as good, may be obtained from olive oil (cold pressed, extra-virgin), almond oil and almond butter, seeds (pumpkin, sesame, and sunflower), avocados, and nuts (particularly walnuts, almonds, and macadamias). Other food choices rich in desirable fatty acids are delineated in the section entitled Essential Fatty Acids in the Therapeutic Section of this protocol.

The Gylcemic Index and Dietary Recommendations

The Glycemic Index lists the relative speed at which different foods are digested and raise blood sugar levels. Each food is compared to the effect of the same amount of pure glucose on the body's blood sugar curve. Glucose itself has a Glycemic Index rating of 100. Foods that are broken down and raise blood glucose levels quickly have higher ratings. The closer to 100, the more the food resembles glucose. The lower the rating, the more gradually that food affects blood sugar levels.

An admonition based more in folk medicine than scientific certainty, that is to avoid the white foods (all sugar-containing foods, rice, and all white flour and flour-based products including pasta), appears to have validity when applied to the Glycemic Index. Common foods bear the following glycemic ratings: baked potatoes, 95; white bread, 95; mashed potatoes, 90; chocolate candy bar, 70; corn, 70; boiled potatoes, 70; bananas, 60; white pasta, 55; unsweetened fruit juice, 40; rye bread, 40; lentils, 30; soy, 15; green vegetables and tomatoes, less than 15.

Some fruits rank lower on the glycemic scale than starchy vegetables, whole grains, and legumes. (Starchy vegetables are potatoes, corn, yams, and most beans.) A serving of low-carbohydrate fruit, that is, grapefruit and unsweetened strawberries, cherries, peaches, and cantaloupe is usually well tolerated.

All sweeteners can be problematic, including honey, high fructose corn syrup (which raises blood glucose levels), and fructose (which increases insulin resistance and triglycerides) (Bland 1983). Carbohydrates found in low-starch vegetables do not encourage a rise in blood glucose levels (e.g., asparagus, broccoli, Brussels sprouts, cabbage, cauliflower, celery, cucumbers, green beans, lettuce, mushrooms, onions, peppers, radishes, spinach, tomatoes, and turnips). It is especially important for an individual with diabetes to learn to read labels. Select foods with no more than 8 grams of carbohydrates per serving, until the condition is well under control. Adding vinegar, lemon juice, acidic fruits, or sourdough bread to a meal slows gastric emptying; consequently, starches and sugars enter the system in a time-released manner (Liljeberg 1996, 1998).

Since large quantities of food are extremely difficult for a diabetic to process, smaller meals are recommended. According to Diabetes Care, moderate amounts of alcohol, that is, no more than 1-2 drinks a day, appear to reduce blood glucose and insulin levels (Facchini et al. 1992). However, exceeding this amount is highly detrimental, increasing both morbidity and mortality. Unfortunately, current studies reflect too many inconsistencies to recommend types of alcohol delivering greater advantage (Rimm et al. 1996).

Sugar-sweetened soft drinks and confections are not permissible for prediabetic or diabetic patients, but the alternative, artificially sweetened beverages and foodstuffs, may not be either. Allegations have implicated aspartame as a potential risk factor for several disorders, although this remains a controversial issue. Many artificial sweeteners (marketed as a sugar substitute) may actually contain sugar, masquerading as dextrose and maltodextrin.

Stevia, an herb considered 100-300 times sweeter than sugar, is often recommended as an alternative to either sugar or aspartame. Because stevia has unusual sweetness, much less is required to provide palatability, and the risk of eliciting an insulin rush is lessened. In fact, various studies suggest that stevia has a regulating affect on the pancreas and could actually assist in stabilizing blood sugar levels. Others contend that yielding to sweet passions by consuming even artificially sweetened products never addresses the problem of sugar cravings. However, enjoying an acceptably sweet treat (on occasion) delivers a significant advantage, dispelling feelings of deprivation and restriction.

Tentative research indicates that men who frequently include hot dogs, bologna, and bacon in their diet increase their risk of Type II diabetes by about 50% (van Dam et al. 2002). While a ban on processed meats is not the objective, moderation is strongly advised.

For example, Dr. Frank Hu (a senior researcher) explained that the risk of diabetes increased when individuals ate processed meats five or more times a week. The data were collected from the Health Professionals Follow-Up Study, a project that began in 1986 by analyzing dietary information from 42,504 men, ages 40-75, who were classified as healthy and free of diabetes, heart disease, or cancer. The men were tracked for 12 years, with the researchers comparing the dietary patterns of those who developed diabetes with those who did not. After attempting to adjust for other less healthy foods that might accompany a hot dog meal, it appeared clear that freely eating processed meats was an independent risk factor for developing diabetes.

A report involving dairy consumption and insulin resistance (appearing in JAMA) attracted widespread media attention. Interest was spiked as researchers showed that diminished milk intake (a trend observed over the past 3 decades) appears to be paralleling an increase in obesity and Type II diabetes. An inverse association was noted between frequency of dairy intake and the development of obesity, abnormal glucose homeostasis, elevated blood pressure, and dyslipidemia in young, overweight, black and Caucasian men and women (Pereira et al. 2002).

Researchers showed that the 10-year incidence of insulin resistance was lower by more than two-thirds among overweight individuals in the highest category of dairy consumption. Although saturated fat contained in dairy products may raise LDL cholesterol in a subset of the population, there are several mechanisms (including milk's position of 34 on the Glycemic Index) that may protect against insulin resistance, obesity, and cardiovascular disease. A positive association was not observed between dairy intake and insulin resistance in individuals who were not overweight (BMI <25) at baseline. Milk is also a source of conjugated linoleic acid (CLA), which has shown anti-obesity effects in numerous studies.

Diabetes Care also reported that the world's most widely used drug may be a hidden key to insulin resistance (Biaggioni et al. 2002; Keijzers et al. 2002). A group of Dutch doctors recruited 21 healthy, lean, nondiabetic men and women under the age of 30 to compare the insulin effects of caffeine and the drug dipyridamole in contrast to a placebo. Dipyridamole is an anticoagulant drug (also known by the name Persantine) that has the opposite effect on hormone arousal compared to caffeine.

The researchers determined that dipyridamole had no effect on insulin sensitivity, but caffeine decreased insulin sensitivity by about 15%. While the numbers may appear insignificant, the decrease is about the same as the increase in insulin sensitivity obtained from typical prescription diabetes drugs. It appears highly probable that the positive effects of Glucophage (metformin) could be cancelled out by few cups of coffee. Moderate caffeine consumption emerges as the recommendation, but if insulin sensitivity is a problem or Type II diabetes is evidenced, zero caffeine consumption appears a wholly worthy gesture.

A variety of phytonutrients derived from spices influence insulin sensitivity (Jarvill-Taylor et al. 2001). For example, American scientists have found that 1 teaspoon of cinnamon a day may help control blood sugar levels. The common spice appears to rekindle the ability of fat cells to respond to insulin and increase glucose removal (Hodge 2000).

The factor found in cinnamon that is responsible for the diabetes advantage is methylhydroxy chalcone polymer (MHCP) (Mercola 2000). Researchers found that MHCP stimulated glucose uptake and glycogen synthesis in a fashion similar to insulin. Dr. Richard A. Anderson (lead scientist at the Beltsville, Maryland-based Human Nutrition Research Centers, a branch of the U.S. Department of Agriculture) said: "Patients could try adding 1/4 to 1 teaspoon of cinnamon to their food" (IBN 2000). It is possible that nothing positive will come from the addition, but it is also biologically conceivable the beneficial effects could prove dramatic.

Exercise: Helpful in Blood Glucose Control

Physical activity plays an extremely important role in overturning the clusters of symptoms (obesity, insulin resistance, and hyperinsulinemia) that accompany diabetes. Exercise need not be unpleasantly aggressive to be beneficial. Focusing on an activity you enjoy and incorporating it into daily activities can be as pleasant as it is gratifying. Whatever the exercise, the participants can take delight in knowing they are burning calories and reducing body fat, triglycerides, cholesterol, blood glucose, and blood pressure, while increasing insulin sensitivity, improving mental outlook, and building muscle and strength.

A retrospective study reported in the New England Journal of Medicine tracked 5990 men over 14 years, monitoring lifestyle and health status of participants. From those numbers, 202 subjects became diabetics. Researchers found that as energy expenditure increased, the incidence of diabetes decreased. For each 500-kcal increment in energy expenditure, the age-adjusted risk of Type II

diabetes decreased by 6%. The protective effect of exercise is strongest in individuals most prone to develop the disease: those persons who are obese, hypertensive, or born to diabetic parents (Helmrich 1991).

A part of the exercise-induced improvement in blood glucose control is explained by looking at the nature of muscles. Muscles are more responsive than fat cells to insulin and glucose, and conditioned muscles are more responsive than unconditioned (Challem 2000). Toned and developed muscles enhance the body's sensitivity to insulin, a process that assists in blood glucose control. Also, Dr. Charles Lardinois, an endocrinologist at the University of Nevada and medical director of the Nevada Diabetes Association (speaking at the ACAM Conference in Nashville, 2001), added that skeletal muscles have a unique ability to take up glucose without the need of insulin. Glucose transporters, known as GLUT-4, regulate the process. Regular exercise induces a greater expression of GLUT-4, thus lowering blood sugar and improving insulin sensitivity.

The exercise advantage was exemplified in the Nurses' and Physicians' Health Studies, showing that physically fit people secrete less insulin after a carbohydrate load (50 grams). Those who exercised at least once a week had one-third less diabetes; studies from Finland confirmed that individuals randomized to an exercise program have a dramatic decrease in the risk of developing diabetes (Manson et al. 1991; Manson et al. 1992; Uusitupa et al. 2000).

A meta-analysis of 14 studies reported in JAMA allowed researchers to systematically review the effect of exercise intervention on glycemic control as measured by HbA1c and Body Mass Index (BMI). Studies in which the intervention consisted only of recommending increased physical activity were not included because it would be impossible to quantify the exercise intervention or compliance. The intervention had to be verified by direct supervision or through exercise diaries. The conclusion of the study was that exercise training reduces HbA1c by an amount that should decrease the risk of diabetic complications. No significant change in body mass was found between the exercise group and those acting as controls (Boule et al. 2001).

Exercise is extremely important to the dieter since there are two fundamental ways to lose weight: by increasing energy output or decreasing energy input. Simply stated, weight is lost by either exercising more or eating less. A small weight loss (even as little as 10 pounds) can often stabilize blood glucose levels and lessen the risk of diabetes. Some estimate regular exercise will reduce the insulin requirements of obese Type II diabetics by up to 100% when combined with weight reduction (Nieman 1995; Blake 2002).

As important as exercise is to the diabetic, it appears equally important to temper physical activity with appropriate amounts of rest, according to information presented at the American Diabetes Association's 61st Annual Scientific Sessions. Dr. Eve van Cauter (University of Chicago) found that chronic sleep deprivation of 6.5 hours or less each night had the same effect on insulin resistance as aging. Healthy adults who averaged 316 minutes of sleep each night (about 5.2 hours over 8 consecutive nights) secreted 50% more insulin than those who rested about 8 hours a night (Ford-Martin 2001; Mercola 2001).

STRESS (THE NEMESIS)

Countless studies caution that stress is expensive; buying into unresolved stress can lead to Syndrome X and diabetes and, if not controlled, to a shorter lifespan. A study conducted at the Mount Sinai School of Medicine showed that stress was one arm of multiple factors that strongly influence hyperinsulinemia (Heller et al. 1995).

Anxious individuals spur the sympathetic nervous system (SNS) into heightened activity, and the adrenal glands leap to respond. The medulla, the inner portion of the adrenal gland, secretes epinephrine (also referred to as adrenaline), a hormone that has significant influence over blood glucose levels. Epinephrine favors the breakdown of glycogen to glucose (glycogenolysis). In a diabetic, the additional glycogen input cannot be utilized and results in elevated blood sugar.

During periods of emotional upheaval, the chief glucocorticoid hormone, cortisol (secreted by the adrenal cortex), is also revved into action. Cortisol lessens the ability of insulin to carry glucose, a transport essential to glucose utilization. The hyperresponsiveness of epinephrine and cortisol reduces the ability of tissues to use glucose and increases the rate of protein conversion to glucose. As cortisol levels increase, DHEA (a hormone, commonly suppressed in insulin resistance) also diminishes.

Stress robs the body of essential nutrients. Diabetes and hyperglycemia, conditions fueled by stress, activate homeostatic mechanisms including polyuria (increased urination to transport sugar from the system). In the process of excreting fluids, water-soluble nutrients are also lost, many of which are essential to stress reduction and glucose management.

Stress contributes to obesity (a factor associated with Syndrome X and Type II diabetes). A stressful person often eats not because of hunger but as a reprieve from demanding, unpleasant situations. Tasty treats temporarily pacify a troubled spirit, but while the stressful individual is overeating, physical changes are occurring. If the foodstuffs have been largely carbohydrate (particularly sugar-based products), free radicals proliferate, a situation biologically similar to being exposed to radiation, cigarette smoke, or air pollution (Challam 2000). As glucose piles up in the bloodstream, the pancreas pumps out insulin to oppose the rise in glucose. The insulin release from the pancreas may be too much, and blood glucose levels plummet to hypoglycemic lows.

Because of homeostatic mechanisms, the brain transmits hunger signals in an attempt to regain strength and inner balance. If the food selected is an insulin-provoking product (such as another sugary treat or foods high on the glycemic scale), the cycle starts anew. Stress was the initiator in the eating frenzy; unstable blood glucose is too often the consequence.

C-Reactive Protein and Cytokines

C-reactive protein (CRP), a protein present in many acute inflammatory conditions, is a significant risk factor in cardiovascular disease. A growing body of evidence indicates that higher levels of CRP may also play a role in central abdominal obesity and the onset of Type II diabetes.

Researchers reported that among 159 men (ages 22-63), body fat increased as CRP levels rose (Lemieux et al. 2001). JAMA reported that men with high fasting insulin levels, as well as individuals with hyperglycemia following a 75-gram glucose challenge, often have elevated CRP levels. Interleukin 6 (IL-6), a cytokine derived from fibroblasts and macrophages, was incriminated (along with CRP) as being predictive of the development of Type II diabetes (Pradhan et al. 2001).

It appears that abdominal fat is, in fact, a major source of inflammatory cytokines. However, it should be noted that cytokine activation is not restricted to individuals who are morbidly obese. Russell Tracy, Ph.D. (University of Vermont's Laboratory for Clinical Biochemistry Research), declares that individuals who are not obviously overweight may still have a disproportionate amount of visceral fat. The increased risk of insulin resistance and atherosclerotic disease associated with visceral obesity may be explained through upregulation of cytokine secretion (Tracy 2001).

In addition, hyperinsulinemia changes the disposition of cytokines. The liver, receiving instructions from cytokines, releases stored fat and sugar into the bloodstream. As body fat increases, insulin resistance increases, as well. Self-perpetuating imbalances slam the body from several directions.

The safest and surest way to overcome this untoward situation is by losing weight. Women completing a 12-week, low-fat, energy-restricted diet lost an average of 7.9 kg (17.4 pounds) and their CRP levels dropped by 26% (Heilbronn et al. 2001). This finding is extremely important because women with the highest serum CRP levels appear about 15.7 times more likely to develop Type II diabetes compared to those with the lowest levels (Pradhan et al. 2001). In addition, French researchers showed that a weight loss resulted in a significant decrease in IL-6 levels (Bastard et al. 2000). Individuals should request hs-CRP testing to

evaluate inflammation as a contributor to diabetes and its progression. Note: hs denotes high sensitivity, the only method able to discriminate subtle differences in CRP concentrations (those that go undetected by standard testing).

Aspirin, fish oil, and vitamins C and E, as well as pravastatin (and other statin drugs), reduce high levels of CRP. IL-6 is lowered by DHEA and vitamin K supplementation. A comprehensive program directed toward lowering proinflammatory cytokines is presented in the Inflammation: Chronic protocol.

DOES TESTOSTERONE PLAY A ROLE IN TYPE II DIABETES?

Testosterone, a hormone produced by both men and women, is not new to endocrinologists as a treatment for diabetes. European clinicians have used testosterone to treat severe cases of diabetes since the 1960s and 1970s. Supplementing to normal testosterone levels of a healthy 25- to 30-year-old man raises HDL cholesterol and reduces blood pressure, triglycerides, and abdominal obesity. However, of equal importance, testosterone appears to lower blood glucose and insulin levels, along with HbA1c (a reflection of blood glucose levels over the last 2-3 months).

Edward M. Lichten, M.D., voiced excitement concerning testosterone's ability to stabilize blood sugar levels, citing near miraculous results, evidenced by the following case studies:

- A 43-year-old male experienced a drop in blood sugar levels from 450 mg/dL to 160 mg/dL in 6 weeks. Insulin requirements were adjusted from 100 units a day to 50 units. Treatment consisted of testosterone pellets implanted in subcutaneous tissue.
- A 53-year-old male realized a drop in HbA1c from 9.9 to 5.5 in 4 months using injectable testosterone 2 times a month; subject was previously treated with Glucophage and Glynase.

Dr. Lichten declared that testosterone might be fixing a defect that develops in a diabetic's body. If, however, diabetes has progressed to an advanced stage in which multiple complications have arisen, testosterone is not the complete answer. Dr. Lichten cautions that the time for intervention is before severe complications develop.

On numerous occasions, Dr. Lichten has been able to eliminate antidiabetic drugs and, in some cases, the need for insulin injections among his patients. This is explainable, in part, because normal levels of free testosterone decrease the need for insulin. Dr. Lichten says that blood glucose control is the primary concern in diabetic management, but the pathophysiology of insulin appears the determinant in diabetic survival.

Dr. Lichten states that his research has established a definite relationship between the amount of free testosterone in the bloodstream and sensitivity to insulin. Healthy men show higher levels of free testosterone and lower sex hormone-binding globulin (SHBG) levels. A nondiabetic male teenager may have a free testosterone of 2 in relationship to SHBG; an 80-year-old man with diabetes and on dialysis may have a free testosterone level of 0.1-0.2.

Men with disease and aging also have an increase in testosterone blockers such as estrogen and SHBG that neutralize or bind testosterone. SHBG amplifies estrogen by preferentially tying up testosterone; in fact, estrogen turns off the brain's signals to supply testosterone.

Dr. Lichten uses pellets (having a 6- to 12-week life) implanted in subcutaneous tissue or injections administered every other week to reestablish testosterone levels. Testosterone can also be administered topically, applying creams, gels, and patches, but the injection route used by Dr. Lichten provides a higher dose. A complete blood count, PSA (prostate specific antigen), DRE (digital rectal examination), and an SMA 12 (to track liver function and lipid values) are among a battery of tests routinely ordered. For information concerning safely increasing testosterone levels in men, refer to the Male Hormone Modulation protocol.

In women, a relative hyperandrogenicity is statistically associated with insulin resistance and centralization of body fat, which are predictors for the development of noninsulin-dependent diabetes

mellitus. Newborn female rats undergoing androgenization (high doses of testosterone) experienced similar developmental patterns, that is, insulin resistance and changes in adipose tissue distribution (Nilsson et al. 1998).

Researchers reporting in the journal Diabetes agreed that administering testosterone to a group of oophorectomized female rats, those having one or both ovaries removed, resulted in a decrease in whole-body insulin-mediated glucose uptake (Rincon et al. 1996). In an unrelated study, researchers from Kaiser Permanente (Oakland, CA) announced that estrogen replacement therapy might prove beneficial in maintaining glycemic control in older women with Type II diabetes. Mean HbA1c levels were significantly lower in women using hormone replacement therapy compared to women not receiving the treatment (Ferrara et al. 2001).

Note: Indian researchers investigated the effects of long-term administration of testosterone enanthate, a derivative of primary endogenous androgen testosterone. Researchers evaluated testosterone enanthate's effects on glucose metabolism including glucose tolerance and fasting serum insulin levels in adult rhesus monkeys. Significant changes in glucose tolerance were not seen in animals treated with testosterone therapy; however, serum insulin levels decreased significantly from months 27-32 of treatment (Tyagi et al. 1999).

DOES SMOKING CONTRIBUTE TO DIABETES?

Cigarette smokers have increased insulin resistance and hyperinsulinemia, higher triglyceride levels, and lower HDL cholesterol compared to nonsmokers. Researchers from Stanford University assembled 40 healthy volunteers (20 nonsmokers and 20 individuals who had smoked at least one pack of cigarettes for 6 years) (Facchini et al. 1992). The smokers showed more insulin resistance, higher levels of circulating insulin, and slightly higher blood glucose levels compared to nonsmokers. Triglyceride-rich VLDL increased by more than 40% and HDL cholesterol levels fell by about 23% among the smokers. According to information released from the 15th World No Tobacco Day, the negatives associated with chronic smoking (20 cigarettes a day) are long lasting; the ill effects endure beyond the actual smoking experience.

There is overwhelming evidence linking active smoking to periodontal disease, a newer risk factor for diabetes, according to Sara G. Grossi, D.D.S. (University at Buffalo senior research scientist and chief researcher in the study). Dr. Grossi announced that even exposure to passive tobacco smoke increases the risk of periodontal disease up to 70%. Gum detachment and the incidence of bleeding gums increased 1.5- to 2.5-fold. The researchers concluded that smoking and exposure to passive smoke should be considered a risk factor for periodontal disease; gum disease, in turn, increases the risk of developing diabetes and makes blood glucose control more difficult in confirmed diabetics (Baker 1999b).

DRUG AND NUTRIENT INFLUENCE ON DIABETES

Some beta-blockers, diuretics, antipsychotic, and sulfonylurea drugs appear to increase insulin resistance and the risk of developing (or worsening) diabetes mellitus (Lithell et al. 1996; Lukaczer 1999; Hagg et al. 2001). Unfortunately, the majority of drugs used to treat hyperglycemia stimulates the pancreas to produce more and more insulin. While this temporarily lowers blood glucose levels, it ultimately further degrades the cells' receptivity and hastens pancreatic exhaustion.

Most calcium channel blockers (used to reduce blood pressure) are seen as neutral in regard to increasing or decreasing insulin sensitivity. Captopril, an angiotensin-converting enzyme (ACE) inhibitor, appears to actually improve insulin sensitivity while lowering blood pressure. The New England Journal of Medicine reported that another angiotensin II receptor blocker (Avapro or the generic Irbesartan) is effective in protecting against diabetic nephropathy. This protection is independent of the reduction in blood pressure that Irbesartan typically causes (Lewis 2001).

The ACE inhibitor ramipril (brand name Altace) may prove to be of particular advantage to diabetic patients. Over the 4.5 years of the HOPE project (a study to determine the effectiveness of ACE inhibitors in preventing cardiac disease), the

number of patients who developed new diabetes in the ramipril group was one-third that of the placebo group. If it can be substantiated that the incidence of diabetes is reduced during ramipril usage, it would indicate that the renin-angiotensin system is also involved in the pathogenesis of diabetes (Yusuf et al. 2000). With drug options, hypertensive individuals who are at a high risk for diabetes mellitus should be steadfast about requesting a drug with a dual purpose: the ability to lower blood pressure and simultaneously increase insulin sensitivity.

Pravastatin (Pravachol®), a cholesterol-lowering drug, also appears to cut the risk of diabetes. The West of Scotland Coronary Prevention Study found that of the 5974 men enrolled in the trial and taking pravastatin, 153 subjects developed diabetes. Researchers concluded that pravastatin therapy resulted in a 30% reduction in the hazard of becoming diabetic. By lowering plasma triglyceride levels, pravastatin therapy may favorably influence the development of diabetes, but other explanations such as the anti-inflammatory properties of the drug in combination with its endothelial effects cannot be excluded with these analyses (Freeman 2001).

It has been determined that some diabetics are low in zinc, a deficiency that may decrease insulin's responsiveness (Faure et al. 1992). However, in a small study, administering 220 mg of zinc sulfate (90 mg of actual zinc), 3 times a day for 2 months, increased fasting glucose rose from an average of 177 mg/dL to 207 mg/dL (Raz et al. 1989). Glycosylated hemoglobin levels also increased among a group of Type I diabetics (not the focus of this protocol) receiving 50 mg of zinc a day (Cunningham 1994). Considering these poor statistics, if more than 15 mg of zinc (the RDA) is used a day, close glucose monitoring must accompany supplementation.

Iron is another mineral that may cause problems with blood sugar. Increased iron stores appear to predict the development of Type II diabetes (and diabetic complications) while iron depletion is protective (Fernandez-Real 2002). In a study involving 18 Type II diabetics with relatively high blood sugar, nine (50%) had elevated serum ferritin levels, the stored form of iron. Researchers found that lowering elevated ferritin levels correlated well with diabetes control and improved fasting glucose, triglycerides, and HbA1c in eight of the nine patients (Cutler 1989).

- Note: According to isolated reports, restoring normal iron levels reversed diabetic conditions in a small subset of patients (Pharmacist 2000). Request that your iron level be checked if you have a blood glucose problem. (The standard reference range for iron is up to 180 mg/dL; less than 100 mg/dL is considered optimal.) A blood test to measure ferritin is a more accurate way of assessing iron levels than relying upon a standard blood chemistry test. In addition, the gene for hemochromatosis was discovered in the mid-1990s. A relatively new DNA test called HLA-H, or more commonly HFE or Hfe, is available for comprehensive testing.

Certain antidiabetic botanicals function by increasing levels of insulin. This process is contraindicated in individuals with existing high insulin levels. Only if the pancreas fails to supply enough insulin should these herbals be used. The Therapeutic Section of this protocol denotes those herbals that work at the level of the beta cells, the insulin factories.

WHEN SHOULD A DIABETIC PATIENT START INSULIN THERAPY?

- Glucose Sensor Implants
- Return to Health

Insulin injections have been relegated to a therapy of last resort in patients with Type II diabetes. This was not always true. In the 1970s, insulin was regularly used to reduce blood glucose levels, sometimes by as much as 30-40 mg/dL. According to a report in JAMA, better glucose control resulted in fewer cardiovascular events occurring among insulin-dependent patients, but (unfortunately) insulin failed to impact the overall death rate (Knatterud et al. 1978).

According to Zachery Bloomgarden, M.D., insulin resulted in a 10-year mean HbA1c level of 7.1% compared with 7.9% in a group not treated with insulin. Hypoglycemia, however, occurred in 37% of patients on insulin, exceeding the 11% who experienced hypoglycemia on chlorpropamide (a

first-generation sulfonylurea) and the 18% on glyburide (a second-generation sulfonylurea). Mean weight gain was 6.5 kg over 10 years among insulin users compared to 4.2 kg on chlorpropamide and 5.1 kg on glyburide (1 kg is equal to 2.2 pounds of body weight) (Bloomgarden 2001). Comment: Sulfonylurea drugs stimulate insulin secretion from islet cells; about 30% of patients fail treatment due to beta cell exhaustion.

Refractory hyperglycemia may require insulin therapy to control blood glucose levels, but until the individual has attempted lifestyle modification, insulin appears a poor first choice. Information appearing in the Washington Post (August 9, 2001, page A1) stated that nearly 60% of those who are poised to develop diabetes can avert the disease (and insulin therapy) through lifestyle modification.

Glucose Sensor Implants

Regular, home blood-glucose monitoring is at the core of diabetes control, determining the severity of the peaks and valleys and their duration. Checking blood sugar levels allows the patient to take appropriate actions if glucose is too high. Preventing chronic hyperglycemia warrants a more favorable outcome for the patient.

The patient may participate in a process called covering, that is, administering rapid-acting insulin (e.g., Lispro) to blunt the damage inflicted by long-term exposure to high glucose levels. When covering is not an option, having a glucose read-out allows the physician to adjust the insulin dosage accordingly. A study released by NIH in 1993 showed that tight glucose control could possibly avert 60% of all long-term complications arising from diabetes.

W. Blake Martin (Vanderbilt University) voiced the need for a type of glucose monitoring that employs user-friendly technology. A study conducted at the University of Wisconsin raises hope that glucose sensors may be the answer. Sensors, lasting from 3-5 months, were implanted under the skin of dogs made diabetic for experimentation. Seven days postimplant, the sensors were continuously monitoring, scrutinizing blood glucose levels during periods of glucose infusions and insulin injections. This type of subcutaneous glucose sensor appears to be promising as a continuous and painless long-term method for monitoring blood glucose. Sensors with top-layer materials that stimulate angiogenesis (blood vessel formation) at the sensor/tissue interface may have better measurement ranges and longer life than previously reported sensors (Updike et al. 2000).

Become a Participant in Your Return to Health

Some conditions are better managed with conventional medicine, and others have a better success rate using a natural approach. Type II diabetes appears to have an affinity for the natural, with remarkable gains reported. However, natural methods have little chance of succeeding without patient participation. This means the patient must refuse inappropriate foodstuffs, make time for exercise, and maintain weight within healthy standards. Diabetics should never blame themselves for their illness, but when the condition becomes manageable, the patient can justifiably claim much of the credit.

Results of the Finnish Diabetes Prevention Study (presented at the American Diabetes Association's 60th Annual Scientific Session in June 2000) illustrate the patient principle, i.e., the patient accepting much of the responsibility for the outcome of the disease process. The study showed that lifestyle modification (a structured dietary and exercise program) reduced the incidence of Type II diabetes by 58% in people at high risk for the disease.

The trial participants (522 prediabetic adults, 172 men and 350 women; average age 55 years) were divided into two groups and tracked over a 5-year period (1993-1998). Frequent dietary advice along with an individualized exercise program that included at least three supervised exercise sessions a week was assigned to the intervention group. The remainder of the individuals (acting as a control group) received nutritional tutorage at a yearly meeting and encouragement to upgrade their exercise regime. The weight reduction was about 4.2 kg at 1 year in the intervention group compared to 0.8 kg in the control group. Some backsliding occurred by the end of the second year in the intervention group, resulting in a 3.5-kg overall net weight loss; the control group's weight loss remained constant at 0.8 kg the second year.

At 1 year, the intervention group showed significantly greater reductions in 2-hour glucose, fasting, and insulin levels, as well as blood pressure and serum triglyceride levels. Most of the beneficial changes in cardiovascular risk factors were sustained for 2 years. The researchers concluded that Type II diabetes is preventable in high risk patients by lifestyle modification (Uusitupa et al. 2000; Tuomilehto et al. 2001).

Self-improvement programs, when faithfully approached, are more rewarding than easy. However, behavioral modification has proved successful in helping more people lose weight than any other kind of weight-loss program. Successful attempts at lifestyle modification should include family members and friends. Recall the number of social gatherings planned around carbohydrates. Sugary treats are foods for celebrating, partying, and showing affection. Finding alternatives to sugar is as possible as it is profitable, and the health dividends far more gratifying.

TREATMENT OPTIONS FOR SYNDROME X AND TYPE II DIABETES

Syndrome X is the term used to describe a variety of metabolic disturbances often seen in persons diagnosed with Type II diabetes. It is important for the Type II diabetic to treat all Syndrome X imbalances by lowering elevated triglycerides and blood pressure, while attempting to increase HDL levels. However, it is imperative for the Type II diabetic to address the primary conditions of insulin resistance, hyperinsulinemia, and hyperglycemia.

The following section, the Therapeutic Section, highlights nutrients and herbs that have won favor as antidiabetic agents. For example, the Helicon Foundation announced in 2000 that it may be possible to address dysfunctions that conspire to maintain hyperglycemia in Type II diabetes by ingesting specific supplemental nutrients such as chromium (for skeletal muscle insulin resistance), conjugated linoleic acid (for adipocyte insulin resistance), biotin (for excessive hepatic glucose output), and coenzyme Q10 (for beta cell function) (McCarty 1999, 2000). These and many other antidiabetic agents (found in natural pharmacology) are fully discussed in this section.

Although the material presented in the Therapeutic Section is well substantiated, diabetes represents a gravely serious condition, requiring a physician to structure the program and monitor progress. However, the patient must be a major team player to expect success. It is extremely important to note (before embarking on any diabetic regime) that the first treatment for Type II diabetes is always diet. Regardless as to whether natural agents or pharmaceuticals are used, dietary restraints are essential to enact change.

Therapeutic Section

- Alpha-Lipoic Acid
- Aminoguanidine
- Bilberry
- Biotin
- L-Carnitine
- Carnosine and a Glycation Review
- Chromium
- Coenzyme Q10
- Conjugated Linoleic Acid
- DHEA
- Essential Fatty Acids
- Fiber
- Magnesium
- N-Acetyl-L-Cysteine
- Silymarin
- Vitamin C
- Vitamin E
- Vitamin K

Nutritional Interventions for the Prevention and Treatment of Syndrome X and Type II Diabetes
Supplemental suggestions are arranged in alphabetical order for easy reference, not in order of importance. Although the nutrients profiled perform multiple functions, only the activities of the supplement relative to Type II diabetes have been included in this material.

It is important for the patient to understand that there are multiple pathological factors involved in common diabetic complications such as neuropathy, blindness, arteriosclerosis, renal failure, and so forth. It is therefore necessary to guard against as many of these underlying mechanisms as is practical to avoid experiencing debilitating and lethal diabetic consequences.

The most important therapeutic modality in the control of Type II diabetes is weight loss. Therefore, the reader is advised to consult the Obesity protocol, which provides innovative methods of reducing excess body fat, while suppressing elevated levels of serum insulin (hyperinsulinemia).

Alpha-Lipoic Acid--lowers blood glucose and insulin levels, reduces insulin resistance, and improves insulin sensitivity

Alpha-lipoic acid, a sulfur-containing compound, may prove to be the "kingpin" in the fight against Type II diabetes and its many complications. Lipoic acid comes with impressive credentials, including the ability to increase the burning of glucose (Challem et al. 2000; Hinderliter 2002). The mitochondria (the powerhouses of the cell) are one of the benefactors of enhanced glucose utilization. This occurs via the Krebs's cycle, a process that utilizes glucose, amino acids, and fatty acids to yield high energy. Lipoic acid intervenes at several points in the Krebs's cycle, warranting a continuous supply of energy to the cell. Free radicals are produced as a byproduct of the energy generated during the Krebs's cycle, but alpha-lipoic acid appears to quench abhorrent free radicals that are not contained during the reactions.

Greater efficiency in the Krebs's cycle results in increased amounts of glucose used for energy production. This is very important for the diabetic: if glucose is used purposely, lesser amounts appear in the bloodstream. Also, the more glucose that is burned, the less insulin your body will have to provide. Lipoic acid resulted in a 50% increase in insulin-stimulated glucose disposal and a significant improvement in insulin sensitivity compared to a nonsupplemented placebo group (Jacob 1995, 1996, 1997). Alpha-lipoic acid appears able to deliver glucose into cells in ways independent of insulin participation. Researchers found that when lipoic acid was injected into fasting nondiabetics or diabetic rats, a rapid reduction in blood glucose occurred without a corresponding effect upon circulating insulin levels (Khamaisi et al. 1999).

Interestingly, lipoic acid protects not only against the damage that causes diabetes, but also against the damage caused by the disease. For example, alpha-lipoic acid guards against blood glucose accumulating in the bloodstream and also protects against the proliferation of free radicals. Oxidative stress is characterized by the excessive generation of free radicals, which injures cells throughout the body. Alpha-lipoic acid helps prevent free radical-induced damage to tissues and organs.

Antioxidants have distinctive characteristics. For example, vitamin C protects only the watery portions of cells from free-radical attack; vitamin E protects fatty membranes. Alpha-lipoic acid possesses antioxidant feats considered extraordinary: the ability to neutralize free radicals occurring in both watery and fatty regions of cells.

Lipoic acid's reputation as the universal antioxidant is justly earned because it unselfishly extends itself to other antioxidants (vitamins C and E, as well as glutathione and CoQ10), regenerating them for continued service and greater efficiency. Acting through its antioxidant powers, lipoic acid appears helpful in reducing the risk of cataracts, as well as increasing blood flow to peripheral nerves (Packer 1994). It is, in fact, approved for the prevention and treatment of diabetic neuropathy in Germany.

Data indicate that lipoic acid is effective in the prevention of early diabetic glomerular injury, proving more effective than high doses of either vitamins A or C (Melhem et al. 2001). (Recall that the kidneys are at particular risk in diabetic patients.)

Glucose increases advanced glycated end products (AGEs). (AGEs are formed when glucose reacts with a protein, damaging the protein in cells, preventing normal function.) Alpha-lipoic acid reduces levels of glycosylated hemoglobin, a standard marker of glucose-damaged proteins (Jain et al. 1998). (To read more about glycation and glycation inhibitors, consult the areas in this section devoted to aminoguanidine, carnosine, chromium, and vitamin C.)

The body makes only small amounts of alpha-lipoic acid; in fact, just enough to avoid deficiency states. By and large, foods that contain mitochondria (such as red meats and organ meats) are regarded as good sources of lipoic acid. According to Lester Packer (head of Membrane Bioenergetics Group at the University of California-Berkeley), other sources

are spinach, potatoes, brewer's yeast, and wheat germ. For most individuals, supplementation appears the most reliable approach to provide therapeutic levels of lipoic acid.

If taken with a full spectrum antioxidant, 250-500 mg a day appear adequate, but diabetics often require larger amounts. For the last 30 years, German practitioners have used 600-1800 mg per day to improve diabetic conditions. Side effects include rare reports of a skin rash, hypoglycemia, and, if chronically used, interference with the actions of biotin. (If the daily dose of alpha-lipoic acid exceeds 100 mg, co-supplement with biotin.) Individuals deficient in vitamins B1 (such as alcohol abusers) and vitamin B12 should emphasize the B vitamins when supplementing with lipoic acid. Because alpha-lipoic acid frequently changes insulin requirements, higher doses should be administered under the observation of a qualified physician.

Aminoguanidine (Pimagedine) and Other Inhibitors of Glycation: Aspirin, ALT-711, and ALT-946

Aminoguanidine appears to forestall the aging process by inhibiting the crosslinking of proteins. An apple slice, untreated and exposed to the environment, typifies the effects of crosslinking: the white fruit under the skin turns brown and loses texture. Diabetes is seen as a form of accelerated aging, with the effects of crosslinking often cited as a cog in its development.

Advanced glycated end products (AGEs) are an offshoot of a reaction occurring between a sugar and a free amino acid. (Free form amino acids are those that have not chained together to form peptides or proteins; they are singular entities.) Glucose is found in every cell of the body and is relatively stable, but it can join with proteins to form a glucose-protein combination. It is this combination that will eventually cause active crosslinks and hasten the aging process.

High glucose levels, even transiently elevated, supply the fuel for the glycation process. The levels of crosslinking products in diabetic patients appear to be 2-3 times higher than among nondiabetics. Compounding the problem, it is speculated that AGEs stay in the body for months, even years, crosslinking with other proteins.

There is emerging evidence that AGEs are potential uremic toxins that play a role in the pathogenesis of renal complications (nephropathy) associated with diabetes (Raj et al. 2000). A number of studies have shown that treatment with aminoguanidine also improves neuropathy (inflammation or degeneration of peripheral nerves) and delays the onset of retinopathy (a noninflammatory eye disorder resulting from changes occurring in retinal blood vessels.)

The good news is that crosslinking is preventable by using glycation inhibitors. For example, aminoguanidine is able to join with substances that cause crosslinks, disrupting the cycle that results in cellular damage. Because aminoguanidine is able to combat many of the complications associated with diabetes, the quality and length of life could be favorably impacted with glycation inhibitors (Friedman et al. 1997).

The importance of inhibiting AGEs was highlighted when Alteon Inc. (January 22, 2001) announced a novel AGE inhibitor, ALT-946. The objective of ALT-946 (now in human clinical development) is to inhibit glycation at the onset. ALT-711, another Alteon compound, targets existing glucose-protein crosslinks, breaking them up after they have formed. A company spokesperson stated that though the rationale is still hypothetical, the intent is to provide a comprehensive approach to control glycation, such as ALT-946 inhibiting new crosslinks and ALT-711 getting rid of old ones.

Researchers found ALT-946 to be more potent than aminoguanidine in preventing AGE's crosslinks in vivo and in vitro. This finding is significant, because heretofore, human clinical trials have shown a meaningful protective effect in diabetic complications, including kidney disease, retinopathy, and dyslipidemia when using aminoguanidine (Imanaga et al. 2000; Forbes et al. 2001; Du et al. 2002).

Since ALT-711 and ALT-946 are not yet available, the value of alternative glycation inhibitors (alpha-lipoic acid, aspirin, carnosine, chromium, and vitamin C) becomes even more relevant. Alteon Inc.

does not project a time frame regarding the availability of their antiglycation products, but in the interim, the company is exploring further clinical development activities for aminoguanidine and proceeding with a preclinical development program for ALT-946 as their second generation AGE formation inhibitor.

Bilberry (Vaccinium myrtillus)--reduces blood glucose levels

According to Linda White, M.D., the fruit of the bilberry bush is a rich source of the bluish pigments called anthocyanidins and proanthocyanidins, two of the many types of flavonoids beneficial in the treatment of diabetes. In The Healing Power of Herbs, Dr. Michael Murray states that oral administration of bilberry reduced blood glucose levels in normal and depancreatized dogs, even when glucose was simultaneously injected (Murray 1995). Italian researchers reported that bilberry consistently decreased blood glucose levels by 26% and triglycerides by 39% in animal models (Cignarella et al. 1996).

Myrtillin appears the most active antidiabetic component in bilberry. An injection of myrtillin, although somewhat weaker than insulin, can be used without threat of toxicity, even at 50 times the recommended dose. The literature indicates bilberry sustains its antidiabetic advantage; that is, postinjection blood glucose levels remained stable for a longer period of time compared to many other hypoglycemic agents (Murray et al. 1991). A suggested oral dosage of bilberry is 100-200 mg, standardized to contain 25% anthocyanidins, 3 times a day.

Biotin--aids in metabolism of macronutrients and glucose utilization and is beneficial in diabetic neuropathy

Biotin, a member of the vitamin B-complex family, assists in the metabolism of fats, proteins, and particularly carbohydrates. Enhanced metabolism is important to the diabetic, who often presents with allergies and food sensitivities, compounding absorption problems.

Biotin directly influences blood glucose levels by working synergistically with insulin to increase the activity of glucokinase, an enzyme responsible for the first step in glucose utilization (Murray 1996). Glucokinase is found concentrated in the liver, but the enzyme is usually very low in diabetic patients. If biotin supplementation is high enough (16,000 mcg/day), the activity of glucokinase is upgraded and a significant improvement in blood glucose control typically occurs (Coggeshall et al. 1985).

Although biotin supplementation plays a pivotal role in blood glucose control, a deficiency is rare. In fact, researchers have found that diabetics have higher levels of biotin (produced by bacteria in the intestines) than nondiabetics. Supplementing with high doses is apparently not correcting a deficiency but rather overcoming a defect in biotin metabolism.

Animal studies indicate that biotin reduces postprandial blood glucose levels and improves insulin's responsiveness (Zhang et al. 1997). Human studies reached similar conclusions, showing that 9 mg (9000 mcg) of biotin a day countered a glucose rise following meals (Maebashi et al. 1993). Diabetic neuropathy, a significant problem among diabetics, also responds well to high dose biotin supplementation (Koutsikos et al. 1990).

A suggested dosage is 8000-16,000 mcg/day for blood glucose management. Biotin is a water-soluble vitamin, meaning it does not accumulate in the body. Toxicity has not been reported, but pregnant and lactating women should avoid high doses.

Biotin food sources, enhancers, and antagonists.

Cooked egg yolk, most fish (especially sardines), liver, poultry, dairy products, beans, and brewer's yeast are good sources of biotin. Enhancers are vitamins B12, folic acid, and B5, along with vitamin C, zinc, magnesium, and high-quality protein. Antagonists to biotin are raw egg whites, sulfa drugs, antibiotics, alcohol, coffee, and the antiseizure medications carbamazepine and primidone.

L-Carnitine--improves blood glucose and HbA1c levels, increases insulin sensitivity and glucose storage, and optimizes fat and carbohydrate metabolism; deficiencies appear allied to cardiomyopathy and diabetic neuropathy

Carnitine is a popular dietary supplement because it has been shown to produce many health benefits.

The following list illustrates its multidirectional value in the treatment of diabetes:

- Carnitine improves insulin sensitivity, increases glucose storage, and optimizes carbohydrate metabolism (Crayhon 1999). A significant effect on whole body insulin-mediated glucose uptake was also observed in normal subjects (Mingrone et al. 1999).
- L-carnitine (200 mg daily), together with chromium (400-600 mcg daily) and moderate caloric restriction, typically results in impressive fat losses (Challem 2000).
- Carnitine appears to protect against diabetic neuropathy. One of the mechanisms of neuropathy is the accumulation of polyols (alcohol) in nerve cells. In animal studies, acetyl-L-carnitine increased nerve carnitine levels and decreased the accumulation of sorbitol (a polyol) in nerves. This finding suggests a close relationship between increased polyol activity and a carnitine deficiency in the development of diabetic neuropathy (Nakamura 1998). Note: Diabetic neuropathy is a noninflammatory process characterized by sensory and/or motor disturbances in the peripheral nervous system. Symptoms (in those even mildly hyperglycemic) can include pain and loss of reflexes in the legs.
- Carnitine deficiency is associated with cataract formation in diabetic patients. A significant loss of carnitine from the lens is observed in diabetic test animals, often foretelling the appearance of a cataract (Pessotto 1997). Because of the increased risk of cardiovascular disease and reduced kidney and liver function in diabetic patients, supplementation with L-carnitine appears warranted (Murray 1996).
- A carnitine deficiency is linked to cardiomyopathy, a condition common among diabetics. In animal studies (6 months after developing diabetes), the myocardial ultrastructure often reveals abnormal-appearing mitochondria, consistent with a carnitine deficiency (Malone 1999). Note: Cardiomyopathy is the partial replacement of heart tissue with a nonfunctional fibrous material that lacks the ability to move blood efficiently.

Many animal and human studies have used acetyl-L-carnitine (the better absorbed and more active form of carnitine) in diabetic trials. Robert Crayhon, a carnitine expert, suggests avoiding carnitine supplements after 3 p.m. to preserve a restful night's sleep. Because increased energy production, a hallmark of carnitine, fosters a greater generation of free radicals, carnitine should always be used with an antioxidant program. A suggested acetyl-L-carnitine dosage is 500-1000 mg twice daily.

Carnosine and a Glycation Review

Glycation, a reaction occurring between proteins and glucose, is recognized as a major contributor to aging and perhaps cancer, as well as the complications arising from diabetes. Glucose provides the fuel for glycation, the insidious protein-glucose combination that (following several steps including the oxidation process) results in the formation of an advanced glycated end product or AGEs. Once AGEs are formed, they interact with neighboring proteins to produce pathological crosslinks that toughen tissues. It has been speculated that no other molecule has the potential toxic effects on proteins as AGEs.

Diabetic individuals form excessive amounts of AGEs earlier in life than nondiabetics, a process that disrupts the normality of organs that depend on flexibility for function. AGEs impair proteins, DNA, and lipids as well as triggering a cascade of destructive events as AGEs cling to cellular binding sites. One of the consequences of AGEs is a 50-fold increase in free-radical formation. Because diabetes (a condition of accelerated aging) spawns a harvest of AGEs, the kidneys are under specific attack.

By opposing glycation, glomerular damage and the resulting inflammation and renal degeneration are reduced. Diabetic rats that were not treated with glycation inhibitors showed a twofold increase in glomerular staining for AGEs compared with a similar group of diabetic rats receiving treatment (Forbes et al. 2001). In addition, glycation inhibitors (protecting against protein damage) are likely to inhibit cataract formation, a complication common to diabetics.

If ever approved by the FDA, glycation inhibitors such as aminoguanidine will enable humans to prevent many of the adversities that accompany

aging. In the interim, carnosine (an amino acid peptide) has demonstrated in several studies to be a safe and effective antiglycating agent. Because carnosine structurally resembles the sites that glycating agents attack, it appears to sacrifice itself to spare the target (Hipkiss et al. 2000). Carnosine also bolsters proteolytic pathways, a function that enhances the disposal of damaged and potentially destructive proteins. A suggested carnosine dosage is 1000 mg/day.

Chromium--modulates blood glucose levels, fights insulin resistance, lowers HbA1c levels, aids weight loss, and inhibits glycation

Anecdotal but confirmed reports of brewer's yeast (a source of chromium) normalizing blood glucose levels hints of chromium's remarkable contribution to diabetic care. Researchers validated the anecdotal stories when the results of a study involving 78 Type II diabetics were published (Bahijiri et al. 2000). One-half of the enrollees received an inorganic chromium (200 mcg a day); the other half received brewer's yeast (supplying 23.3 mcg of chromium per day). Both groups realized a significant decrease in glucose in urine and fasting blood glucose levels as well as after a 2-hour, 75-gram glucose load. In fact, some trial participants were able to decrease antidiabetic drugs, and others no longer required insulin. Interestingly, a higher percentage responded positively to brewer's yeast, presumably because of better absorption; that is, the body retained more of the trace mineral.

The literature teems with similar reports regarding chromium's ability to modulate errant blood glucose levels. In fact, chromium is so important it is considered essential nearly every time you eat. Unfortunately, about 90% of adults are chromium deficient, according to the U.S. Department of Agriculture. (The highest tissue levels of chromium are found in newborns, with the tissue levels dwindling over a lifetime.) The conundrum surrounding chromium is that as chromium becomes deficient, more insulin is required, and as insulin production becomes excessive, a chromium deficiency occurs. In addition, chromium levels are seriously depleted when eating a diet high in refined sugar and white flour products.

It was known by the 1950s that chromium was required by animals to control blood sugar, but it was not until the 1970s that chromium's essential role in humans was clearly proven. The following chance finding established chromium's validity in reducing diabetic symptoms: patients receiving Total Parenteral Nutrition (TPN), a specially prepared feeding solution delivered through the patient's veins, developed high blood sugar in the absence of diabetes. Insulin therapy was begun but without satisfying results. It was determined that the TPN was deficient in amounts of chromium adequate to stave off diabetes-like symptoms. When 50 mcg of chromium were added to their IV feedings, the patients no longer required insulin and their blood glucose levels returned to normal (Mennen 1996).

Several mechanisms render chromium valuable in blood glucose management:

- Chromium is essential in glucose metabolism. Note: It is estimated only about 3% of ingested chromium is absorbed into body tissues. The mineral is stored primarily in the spleen, skin, kidneys, and testes (Whiting 1989).
- Chromium assists in overcoming insulin resistance (McCarty 2000).
- Chromium appears to be involved in the insulin-induced movement of glucose into cells, probably by encouraging the binding of insulin to the receptor site or participating in reactions that occur immediately after the binding process, called postreceptor events.

The results of a 4-month study, presented at the 57th Annual Scientific Session of the American Diabetes Association Meeting in 1997, demonstrated that daily supplementation with 1000 mcg of chromium (supplied as chromium picolinate) significantly enhanced the action of insulin. The trial participants (29 overweight individuals with a family history of diabetes) completed the randomized, double-blind, placebo-controlled clinical trial showing that chromium reduced insulin resistance by 40% over the placebo group. (The study was conducted by William Cefalu, M.D., director of the Diabetes Comprehensive Care and Research Program at the Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, NC.)

High blood glucose damages proteins, a process called glycation. When blood sugar is high, glucose becomes attached to various proteins, including hemoglobin (the oxygen-carrying protein in red blood cells). A protein with glucose attached is said to be glycosylated, and in the case of hemoglobin is measured as HbA1c. Glycation is responsible for many of the complications of diabetes, a process that chromium inhibits.

To assess the effects of chromium on glycosylated hemoglobin levels, 180 Type II diabetes patients were divided into three groups and supplemented daily with 200 mcg of chromium, 1000 mcg of chromium, or a placebo (Baker 1996). After 4 months, there was improvement in both chromium-treated groups. Glycosylated hemoglobin (a measurement of average blood glucose) over a 2- to 3-month period was (on an average) 6.6% in the high dose group, 7.5% in the low-dose group, and 8.5% in the placebo group. For a nondiabetic, HbA1c is normal at 4-6%; for a diabetic, the goal is to maintain HbA1c at less than 7%.

To fully understand the previous study, HbA1c (expressed in percentages) and the blood sugar equivalents (mg/dL) follow:

4.0% = an average of 60 mg/dL of glucose

5.0% = an average of 90 mg/dL of glucose

6.0% = an average of 120 mg/dL of glucose

6.6% = an average of 138 mg/dL of glucose

7.0% = an average of 150 mg/dL of glucose

7.5% = an average of 165 mg/dL of glucose

8.5% = an average of 195 mg/dL of glucose

The data presented show how the HbA1c blood test measures average glucose levels over an extended period of time. When interpreting HbA1c, keep in mind that the results differ depending upon the test method used. Some laboratories measure hemoglobin A1, which is different from A1c. Also, the results may reflect the averaging of a period of high glucose with a period of low glucose as opposed to the consistent readings required for diabetes control.

Unfortunately, chromium supplementation is not as popular as it should be. One of the major problems hindering chromium usage is the fact that deficiencies are not easily gauged. Supplementation, followed by the laboratory assessment of blood glucose levels, appears the best appraisal of chromium's worth.

A chromium dosage of 50-100 mcg daily is high enough to correct a deficiency but not sufficient to improve blood sugar control. Dr. Richard Anderson (a biochemist and nutritionist with the Department of Agriculture) recommends that persons with diabetes and impaired glucose tolerance take 400-600 mcg of chromium daily. (Some practitioners report superior results in treating diabetes with the polynicotinate form of chromium, citing greater absorptive powers as the biological advantage.) Because significant changes in insulin requirements can occur with chromium therapy, physician monitoring is advisable.

- Note: In the mid-1990s, chromium picolinate came under fire when it was linked with chromosome damage. Extensive toxicological testing proved that this indictment was invalid. Multiple trials have shown it is extremely difficult to harm laboratory animals with oral chromium supplementation. The public can be grateful for this because chromium is the chief nutritional barrier between healthy blood glucose levels and diabetes..

Chromium food sources, enhancers, and antagonists.
Brewer's yeast, whole grains, liver, cheese, meat, and potatoes are good sources of chromium. Enhancers are essential amino acids, selenium, and vitamin E. Hemochromatosis (excesses of iron) antagonizes chromium absorption.

Coenzyme Q10--has antioxidant value and may enhance beta cell function and glycemic control
Some researchers credit CoQ10, a lipid soluble antioxidant, with being able to counter much of the oxidative stress imposed by diabetes. However, the results of a study conducted at Indiana University School of Medicine (Bloomington) leaves the question unsettled (Rauscher et al. 2001).

According to one member of the research team, a group of rats with streptozotocin-induced diabetes was treated with CoQ10 (700-mg human equivalent per day) 30 days following inducement and continued for 14 days. Before beginning CoQ10 supplementation, all of the animals were extremely ill, with tissues showing increased oxidative stress and disturbances in oxidative defenses compared to normal controls. Treatment with CoQ10 ameliorated some of the diabetes-induced changes caused by oxidative stress but caused others. For example, treatment with CoQ10 reversed diabetic effects on liver glutathione peroxidase activity, renal superoxide dismutase activity, cardiac lipid peroxidation, and oxidized glutathione concentrations in the brain. However, treatment exacerbated the increase in cardiac catalase activity (which was already elevated in diabetes), further decreased hepatic glutathione reductase activity, augmented the increase in hepatic lipid peroxidation, and further increased glutathione peroxidase activity in the brain and heart. The tradeoff continued on several important parameters.

The Indiana researcher commented that other laboratories administering CoQ10 earlier in the trial had more gratifying results. He also mentioned the brevity of the CoQ10 administration (only 2 weeks) as another mitigating factor. Currently, the Indiana team is using the same model, but adding quercetin (a bioflavonoid) to the CoQ10. It is hoped that the synergistic value of cooperating nutrients will deliver greater therapeutic value.

The Indiana University study is representative of the inclusive results that can manifest when one supplement is examined by itself. Antioxidants (as CoQ10) should be taken with other antioxidants, rather than emphasizing a single factor. Many commercial CoQ10 products are complexed with other antioxidants to balance the effects of CoQ10 at the cellular level.

On the other hand, Japanese researchers gave a favorable nod to CoQ10, citing (among CoQ10's virtues) its ability to enhance beta cell function and improve glycemic control (McCarty 1999). Recall that the Helicon Foundation (San Diego, CA) selected CoQ10 as one of four nutrients (the others are biotin, chromium, and conjugated linoleic acid) as a part of a wholly nutritional therapy against Type II diabetes. A suggested CoQ10 dosage is 100 mg/day. Take higher doses if you have neurological or cardiac impairment.

Conjugated Linoleic Acid--aids in weight management, improves insulin sensitivity, and reduces blood glucose levels

According to information released at the national meeting of the American Chemical Society (ACS) in August 2000, the long-awaited first results of human studies evaluating conjugated linoleic acid (CLA), a naturally occurring fatty acid, indicate that the supplement may help overweight adults lose weight and maintain the loss.

Animal studies have for the past 10 years affirmed CLA's importance in weight management, but human studies were lacking. More recently, human studies (conducted in Norway and the United States) substantiated animal studies, confirming that overweight individuals experienced a statistically significant reduction in body fat while supplementing with CLA. The trial participants did not alter eating habits, and no adverse side effects accompanied supplementation.

It is also speculated that CLA may reduce body fat by increasing energy expenditure. Researchers at the Pennington Biomedical Research Center (Baton Rouge, LA) observed that CLA-fed mice (after only 1 week of dosing) experienced increased energy output, a perk that was sustained 6-weeks postsupplementation (DeLany et al. 2001).

The University of Wisconsin (Madison) released results of a 6-month study involving 89 overweight people. Michael Pariza, Ph.D., one of the researchers, determined that exercise and food restriction initially caused a weight loss but noted that the loss was difficult to maintain. Typically, individuals regained their lost weight at a ratio of 75% fat to 25% lean. Individuals supplementing with CLA were better able to maintain goal weight, with less fat regained and more muscle mass retained (ACS 2000; Pariza 2000).

A team from Purdue University and Pennsylvania State University announced that CLA appears to reduce blood glucose levels and prevent diabetes, at least for the short-term. Animal studies demonstrated that CLA worked as well as a new

class of diabetes-fighting drugs, the thiazolidinediones (TZDs).

Karen Houseknecht (assistant professor of animal studies) at Purdue says that CLA may have advantages over current drug therapies considering overall health benefits. When Zucker Diabetic Fatty rats (those specially bred to become obese and develop glucose intolerance) are given TZD, they become fatter. Conversely, when laboratory animals are given CLA, they become leaner. (During the course of the CLA study, obese animals lost 10% of body fat and lean animals lost 25%.) After 2 weeks, the CLA-supplemented rats were diabetes free; all of the unsupplemented rats had developed diabetes (Houseknecht et al. 1998).

Among 22 individuals enrolled in an 8-week CLA/diabetes study, 64% experienced improved insulin sensitivity (the premier focus in reversing Type II diabetes) while taking 6.0 grams a day of CLA (ACS 2000). Maureen Charron (diabetes researcher and associate professor of biochemistry at the Albert Einstein College of Medicine at Yeshiva University in New York), although excited about CLA as an antidiabetic agent, is tempering her enthusiasm until more studies are completed. In the interim, the Purdue team is considering feeding CLA to hogs to see if the CLA content of pork can be increased. The researchers jest that the ramifications of a pork chop that fights both cancer and diabetes is "emotionally overwhelming" (Houseknecht et al. 1998). A suggested CLA daily dose is 3000-4000 mg, usually four to five 1000-mg (76%) capsules.

Food sources of CLA The polyunsaturated fat is found in meats and cheeses and in lesser amounts in milk, yogurt, poultry, eggs, and cooking oil. (According to Purdue researchers, CLA looks like corn oil, just a little clearer. Note that the CLA content of dairy products and meat is lower than what it used to be because cows primarily eat in feedlots as opposed to eating grass. As a result, CLA supplements have become a popular adjunct weight-loss approach.)

DHEA (Dehydroepiandrosterone)--is beneficial to diabetic and obese individuals, reduces IL-6 levels, and eventually converts to testosterone in some individuals

Although not universally accepted, some studies suggest that high serum insulin predisposes one to low levels of DHEA (Yamaguchi et al. 1998). A fall in serum levels of DHEA is associated with a higher incidence of atherosclerosis and obesity. An association has now been made with diabetes. These observations suggest that DHEA may play a protective role in diseases that gain a stronghold when DHEA levels become low (Lukaczer 1999).

A lack of DHEA appears to be a primary cause of insulin resistance (likely because a DHEA shortage interferes with insulin's ability to regulate blood glucose). Since insulin is one of the hormones that affect fatty acid metabolism, insulin resistance is often observed when fatty acid metabolism is abnormal. Illustrative of this, rats fed a diet containing 0.3% DHEA (ages 5-25 months) had about 25% less body fat than animals not supplemented. Concurrently, the rate of glucose disposal was 30% higher in the DHEA-treated group due to greater insulin responsiveness (Han et al. 1998).

More recently, the dangers of C-reactive protein (CRP), a newer risk factor associated with heart disease, have expanded to include diabetes, with researchers referring to it as a predictive factor for the disease (Pradhan et al. 2001). Since individuals who are obese and insulin resistant often present with higher levels of CRP, addressing CRP levels has become even more relevant for diabetic patients. In addition, elevations in interleukin-6 (IL-6), an inflammatory cytokine, has emerged as another prognostic evaluation for diabetes. Israeli researchers showed that DHEA, an intrinsic neurosteroid, inhibited IL-6 by 95% (Kipper-Galperin et al. 1999).

The kidneys are of significant concern in nonresponsive hyperglycemia. DHEA, a major secretory product of the human adrenal gland, has been shown to possess multitargeted antioxidant activity, including effectiveness against glucose-induced lipid peroxidation. This adaptation protects the kidneys against oxidative damage and impairment of cell growth, suggesting effectiveness

in overcoming chronic renal complications associated with diabetes (Brignardello et al. 2000).

Suggested DHEA dosage and caveats. A suggested dosage is 15-75 mg, taken early in the day (50 mg represents a typical daily dose.) Blood tests are valuable 3-6 weeks into therapy to assist in assigning appropriate dosages. Optimal DHEA levels for men are between 400-560 mcg/dL; for women, the range is considered ideal at 350-430 mcg/dL.

Because DHEA invigorates hormonal systems, it is not recommended for men with prostate cancer or for women with estrogen-dependent cancer, without physician approval. (DHEA can be converted into testosterone and estrogen.) Before starting DHEA therapy, men should know their serum PSA (prostate specific antigen) level and have passed a digital rectal examination (DRE). DHEA does not cause prostate cancer, but because DHEA can cause an increase in testosterone levels, the presence of an undetected cancer should be ruled out before initiating the therapy.

For a comprehensive review of the natural products capable of reducing proinflammatory cytokines, please consult the Inflammation: Chronic protocol. The Cardiovascular Disease protocol contains valuable information regarding the risks imposed by elevated CRP and natural measures to counter it.

Essential Fatty Acids--promote release of prostacyclin, help maintain cell membrane insulin responsiveness, are beneficial to dieters, and lower CRP

Omega-3 fatty acids (alpha-linolenic acid), the parent of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), help maintain healthy cell membranes. This means that the membranes are flexible and contain larger numbers of insulin receptors that are more receptive and responsive to insulin (Lukaczer 1999). Researchers have shown that eating a diet that emphasizes omega-3 fatty acids (herring, mackerel, sea bass, salmon, cod, sardines, fresh tuna, whitefish, coldwater halibut, anchovy, and walnuts) along with monounsaturated fats (olives, almonds, pecans, cashews, filberts, and macadamias) is effective medicine against membrane alterations.

Japanese researchers recently showed that EPA reduced plasma lipids and abdominal fat deposits and increased glucose disposal. Results indicate that long-term feeding of EPA appears effective in preventing insulin resistance in diabetic-prone laboratory animals (in part) by improving blood lipid levels (Minami et al. 2002).

Depressed levels of prostacyclin, a major vasoprotective molecule, are central to the pathogenesis of diabetic neuropathy. Because of inadequate amounts of prostacyclin among diabetics, red blood cells (responsible for oxygen carriage) become brittle and rigid. This prevents oxygen from freely entering the cells, a process that most damages small capillaries and the tissues they serve. Gamma-linolenic acid (GLA), an omega-6 fatty acid, promotes the release of prostacyclin. This function (in turn) adds flexibility to blood cells, regenerates capillaries, and stabilizes nerves (Guivernau et al. 1994; Angilley 2001). Using evening primrose oil (EPO), a good source of GLA, resulted in a 22% increase in endoneural (nerve sheath) capillary density (Cameron 1990). Persons beginning EPO therapy should allow 8-10 weeks to realize a significant effect (Fang 1997; Angilley 2001).

Studies have shown that genetically obese people also profit from essential fatty acid supplementation. The weight loss in these individuals is gradual but reliable, even among those considered intractably obese.

GLA appears to stimulate brown fat cells by producing prostaglandin E1 (PGE1). Brown fat is of particular advantage in maintaining a desirable weight because it uses extra calories to provide heat, preventing the deposit of unsightly white fat. Brown fat's energy-use capacity accounts for major differences between brown fat and white fat. Mitochondria are abundantly dispersed throughout brown fat cells (Braly 1985).

Type II diabetics should supplement with at least 900 mg of GLA a day from borage oil, along with 500 mg of EPA and 1300 mg of DHA from fish oil. Research suggests the DHA fraction of fish oil is particularly effective in reducing CRP (Madsen et al. 2001; Pradhan et al. 2001). This quantity of fatty acids GLA, EPA, and DHA can be obtained in 8

capsules by using highly concentrated borage and fish oil supplements.

Fiber--lowers blood glucose levels

It is difficult to overstate the benefits garnered from fiber in regard to blood glucose control. Eating a diet rich in high fiber foods has spared countless individuals the risks imposed by chronically elevated blood glucose and the rigors of aggressive antidiabetic therapy.

A high fiber diet offers many health benefits, some of which accrue whether the appropriate fiber is selected or not (Hayes 2001). However, therapeutically speaking, fibers are not equal; they have different metabolic dispositions.

The two types of fiber are insoluble (does not disperse in water) and soluble (does dissolve in water). Insoluble fibers are identified as cellulose and many hemicelluloses and lignins; soluble fibers include pectin, gums, mucilages, and some hemicelluloses.

Fibers target different metabolic disturbances. For example, the benefits gleaned from insoluble fibers usually involve the gastrointestinal (GI) tract, promoting bowel regularity, while slowing the breakdown of starch and delaying glucose absorption into the blood. Soluble fibers (the type popularized since the 1980s) slow gastric emptying and the transit of chyme (the semifluid material produced by gastric digestion of food) through the intestines. This function forestalls the quick entry of glucose into the bloodstream. Soluble fibers appear to improve insulin sensitivity and reduce hyperinsulinemia as well. Many of the conditions surrounding Syndrome X, including poor lipid levels and disrupted coagulation factors, are favorably impacted by fiber.

Some people associate fiber with bran products, but dietary fiber also includes the nondigestible portion of plant foods found in whole grains, fruits, vegetables, and dried beans and peas, as well as nuts and seeds. Although fiber cannot be digested and does not supply calories or nutrients, it is far from a purposeless food factor. In addition to direct impact upon various forms of ill health, soluble fibers provide short-chain fatty acids. Bacteria in the human digestive tract ferment fiber, that is, they digest fibers in the absence of oxygen. This process generates water and short-chain fatty acids. The short-chain fatty acids are absorbed in the colon and yield energy when metabolized (depending upon the extent to which they are broken down and absorbed) (Murray 1996). The short-chain fatty acids produced by GI bacteria are primarily acetic acid, propionic acid, and butyric acid (Whitney 1998).

The American Diabetes Association (ADA) recommends that individuals with diabetes consume the same amount of fiber (both soluble and insoluble) as that recommended for the general population: 20-35 grams a day. This recommendation may not be sufficient to stabilize blood glucose levels. The ADA's guidelines for fiber consumption were based on the rationale that 20-35 grams of fiber were a reasonable amount to expect individuals to obtain from dietary sources. (Considering the amount of fast and convenience foods consumed, it is estimated many people consume only 5-17 grams of fiber a day.)

A study reported in the New England Journal of Medicine involved diabetic patients consuming a diet supplying 25 grams of soluble fiber and 25 grams of insoluble. (This amount is about double the amount that is currently recommended by the ADA.) The fiber was derived from foodstuffs, with no emphasis placed on special or unusual fiber-fortified foods or fiber supplements. After 6 weeks, tests revealed that the high fiber diet had reduced blood glucose levels by an average of 10%; equally important, levels of circulating insulin were also reduced (Chandalia et al. 2000).

Fiber is also valuable to persons on diets because it produces a feeling of satiety, negating the desire to overeat. Apart from getting an early sense of fullness, fibrous foods require more chewing; by extending mealtime, the person on a diet is satisfied both physically and emotionally. Because high-fiber foods are digested more slowly, hunger pangs are forestalled. For the most part, fibrous foods represent healthy food (nutrient-dense and low-fat), additional perks for weight watchers.

Fiber should be added slowly, gradually substituting low-fiber foods with high-fiber alternatives. This is necessary for the following reasons: (1) insulin and prescription drugs may have to be adjusted to

accommodate lower blood glucose levels, and (2) without a gradual introduction of the new material, gastric distress could occur.

Some individuals prefer to bolster fiber volume by adding supplemental pectin, gums, and mucilages to each meal. Calculate the amount of fiber gained from foodstuffs and supplement with enough to compensate for shortfalls. Recall that successful trials used soluble and insoluble fibers (a total of 50 grams a day). Monitor blood glucose levels closely to assess gains and to adjust oral or injectable hypoglycemic agents.

High-fiber foods follow (those emphasized in the study in the New England Journal of Medicine), with soluble fiber identified by (S) and insoluble identified by (I) and expressed in grams per serving (Chandalia et al. 2000). (Fiber content of foods was collected from sources apart from the published study.)

Cantaloupe (one-quarter):	(S) 0.13, (I) 0.80
Grapefruit (one-half):	(S) 0.9, (I) 0.4
Raisins (1/4 cup):	(S) 0.22), (I) 1.30
Orange (1 medium):	(S) 0.79, (I) 1.70
Papaya (1 cup):	2 grams total of fiber
Lima beans (1/2 cup):	(S) 0.2, (I) 1.2
Okra (8 pods):	3 grams total of fiber
Sweet potato (one, 5 in. × 2 in.):	3 grams total of fiber
Winter squash (1 cup):	6 grams total of fiber
Zucchini (1/2 cup):	(S) 1.1, (I) 1.4
Oat bran (1/2 cup):	(S) 2.2, (I) 2.2
Oatmeal (1 cup):	(S) 1.64, (I) 2.81

Magnesium--lowers blood glucose levels, increases insulin sensitivity, and calms the sympathetic nervous system

Although the relationship between magnesium and diabetes has been studied for decades, it is still poorly understood. However, what is known about diabetes and magnesium embodies a persuasive list encouraging supplementation:

- Low magnesium levels are common findings in noninsulin-dependent diabetic patients (Paolisso et al. 1989). In fact, diabetes is a frequent cause of secondary hypomagnesemia (lower blood levels of magnesium). Poorly controlled diabetics excrete more magnesium than do nondiabetics.
- Magnesium assists in the maintenance of functional beta cells (insulin factories) (Kowluru et al. 2001). Scientists believe that a magnesium deficiency interrupts insulin secretion and its activity. Magnesium, by enhancing the action of insulin, improves insulin's ability to transport glucose into the cell.
- Magnesium increases the number and sensitivity of insulin receptors (Waterfall 2000).
- An increase in red blood cell magnesium significantly and positively correlated with an increase in both insulin secretion and action. Correction of low erythrocyte magnesium concentrations may allow for improved glucose handling, particularly in elderly diabetic patients (Paolisso et al. 1992, 1993a).
- As magnesium levels plummet, the incidence of diabetic complications escalates. Of particular concern is the association between low magnesium levels and ischemic heart disease and retinopathy. It appears that magnesium may prevent and retard the development of vascular complications common to diabetic patients (Elamin et al. 1990).
- Magnesium not only plays a role in insulin resistance and hypertension, but also plays a role in the correction of carbohydrate intolerance (Murray 1996).

Magnesium is the mineral of choice to reduce hyperresponsiveness occurring in the sympathetic nervous system (SNS). This is important to the diabetic because when the SNS is alerted, blood glucose levels tend to be higher. The SNS is also associated with fostering greater levels of stress and anxiety, earning its reputation as the "flight or fight" division. Since diabetes is considered to be a disease promulgated by stress, supplementation that favors an inner calm is of significant advantage.

Serum magnesium levels are relatively insensitive assessments of magnesium status. Magnesium deficiency is far better detected by measuring mononuclear blood cell magnesium, as opposed to serum levels. A suggested magnesium dosage is 500 mg of elemental magnesium daily along with a diet favoring magnesium-rich foods, for example, whole grain cereals, nuts, legumes, and green vegetables. Since vitamin B6 is intricately involved in

magnesium absorption, at least 30-50 mg of vitamin B6 should accompany magnesium supplementation.

N-Acetyl-L-Cysteine--protects beta cells against free-radical destruction
Free radicals flourish when blood glucose levels are high, causing various forms of tissue destruction in patients. A study examined the involvement of free radicals in the progression of pancreatic cell dysfunction and evaluated the usefulness of N-acetyl-L-cysteine (NAC), a potent antioxidant, to counter the attack (Kaneto et al. 1999). The study was reported in the journal Diabetes and the conclusion was that NAC exerts beneficial effects by preserving beta cell function. This finding supports the implication that free radicals promote beta cell dysfunction and that antioxidant therapy is a useful adjunct in diabetes management.

During NAC therapy, the following observations were made:

- Pancreatic beta cells appeared to be protected against glucose toxicity (Kaneto et al. 1999).
- The insulin-producing beta cell mass was larger in diabetic mice treated with NAC compared to untreated mice (Kaneto et al. 1999).
- Beta cell death was suppressed. The journal Diabetes reported that high levels of glucose appeared to directly upregulate the cell death receptor Fas on human pancreatic beta cells. This finding may explain the loss of beta cell mass observed in Type II diabetes (Donath et al. 2001).
- Glucose-stimulated insulin secretion continued, followed by a modest decrease in blood glucose levels with NAC supplementation (Kaneto et al. 1999).

A suggested NAC dosage is 600 mg a day on an empty stomach for optimal absorption.

- Note: When taking NAC, it is recommended that two to three times as much vitamin C be taken conjunctively because of the prolonged presence of the oxidized form of L-cysteine.

Silymarin--improves liver function and blood glucose control and reduces free-radical activity
The liver performs more than 500 functions, including the regulation of blood glucose. According to information released from the Diabetes Forum (Gopi Memorial Hospital), the liver is the first and most important tissue involved in insulin utilization. In fact, if the liver becomes damaged, secondary diabetes can result. An injured liver is unable to respond to insulin normally and essential blood glucose regulatory systems become less functional. If glycogenolysis (the breakdown of glycogen to supply glucose), gluconeogeneis (the hepatic synthesis of glucose from noncarbohydrate sources), or glycogenesis (the synthesis of glycogen from glucose) is depreciated, tight blood glucose control becomes impossible.

A group of 60 patients with type II diabetes and alcohol-induced liver damage were divided into two groups: for 12 months, 30 received 600 mg per day of silymarin (an antioxidant flavonoid derived from the herb milk thistle) while 30 received a placebo. All subjects were classed as very ill at the onset of the study (Velussi et al. 1997; Challem et al.2000).

Those receiving silymarin evidenced a significant reduction in fasting blood glucose levels (an improvement also mirrored in urine glucose). Initially, average glucosuria (glucose in urine) was 37 grams, dropping to 22 grams during therapy. Fasting glucose levels rose slightly during the first month of supplementation but declined thereafter from an average of 190 mg/dL to 174 mg/dL. As daily glucose levels dropped (from an average of 202 mg/dL to 172 mg/dL), HbA1c also substantially decreased. Throughout the course of treatment, fasting insulin levels declined by almost one-half and daily insulin requirements decreased by about 24%. Liver enzymes (SGOT and SGPT) modulated, reflecting improved liver function. A lack of hypoglycemic episodes suggests silymarin not only lowers blood glucose levels, but also stabilizes them as well. Glucosuria, fasting insulin, and glucose levels, as well as HbA1c, remained unchanged in the nonsupplemented group.

In an 8-day, cell-culture study, German researchers found that a specific silymarin flavonoid, silibinin, prevented the accumulation of fibronectin protein in kidney cells. (Fibronectin is one of the principal

causes of kidney damage in diabetics.) Simone Wenzel, Ph.D., incubated human mesangial cells (a type of kidney cell) in high concentrations of glucose or in a combination of glucose and silibinin. An accumulation of fibronectin was prevented, with protection attributed to silibinin's antioxidant properties (Wenzel et al. 1996).

Silibinin is the most active constituent of silymarin and is sold as a drug in Germany to treat hepatic disorders. Standardized milk thistle extract usually consists of 35% silibinin, whereas the silymarin concentrate used in Europe contains a minimum of 80% silibinin. A suggested silymarin dosage for Syndrome X patients (those not yet diagnosed with diabetes) is a supplement that provides 250 mg a day of silibinin and 60 mg of silymarin. Diabetic patients often take 2-3 silibinin/silymarin capsules providing the same amounts.

Vitamin C--lowers blood glucose and CRP levels, inhibits glycation, prevents accumulation of sorbitol, and protects against free radicals

An exchange occurring between hormones and nutrients maintains health at the cellular level. For example, insulin (by facilitating the transport of vitamin C into cells) decreases capillary permeability and aids in wound healing. Diabetics are often deficient in intracellular vitamin C; this deficiency deprives a diabetic of the protection this important nutrient delivers (Sinclair 1994).

- Vitamin C, an antioxidant, protects against free-radical activity, which is notoriously aggressive in diabetic patients.
- Vitamin C makes blood glucose management easier. Vitamin C deficiencies increase HbA1c (an average measurement of blood glucose levels over the last several weeks) (Sargeant 2000).
- Vitamin C inhibits glycation, a destructive process that occurs when glucose reacts with a protein (Emekli 1996; Vincent 1999). The glycosylation of proteins in red blood cells, the lens of the eye, and nerve cells causes abnormal structure and function of cells and tissues. This untoward sequence contributes to many of the complications common to diabetes (Brownlee et al. 1984).
- C-reactive protein (CRP) is higher in individuals with clinical evidence of insulin resistance. It appears some of the increase in winter cardiovascular mortality may be related not only to a rise in fibrinogen, but also to an increase in other inflammatory markers, such as CRP. This cycle may be spurred as winter infections increase and vitamin C intake decreases because of less availability of fruits and vegetables (Khaw et al. 1997).
- Vitamin C might be able to influence cardiovascular and diabetic risks by modulating the inflammatory response to infection.
- Vitamin C reduces sorbitol accumulating within the cell and the risk of diabetic complications, including cataracts (Murray 1996).

Administering vitamin C in amounts of 1000-3000 mg daily (in divided doses) has been shown to significantly improve a diabetic's prognosis.

Food sources of vitamin C, enhancers, and antagonists

Fresh vegetables and fruits (particularly citrus) are excellent sources of vitamin C. Bioflavonoids are vitamin C enhancers. Antibiotics, antihistamines, steroid drugs, birth control pills, tobacco, stress, and aspirin are vitamin C antagonists.

Vitamin E--reduces C-reactive protein (CRP) and oxidative stress, enhances insulin sensitivity and glucose transport, and prevents complications arising from inflammation

Vitamin E's antioxidant properties and its ability to enhance insulin's responsiveness are but a few of the reasons the nutrient should be included in a diabetic protocol. This was clearly evidenced in a 4-month study reported in the American Journal of Clinical Nutrition with subjects receiving (approximately) 900 mg of vitamin E a day. The researchers assessed how well 15 Type II diabetics and 10 healthy controls tolerated glucose before and after vitamin E supplementation. In healthy subjects, glucose removal from the blood increased 17%. In diabetics, total glucose removal increased 47% and nonoxidative glucose metabolism increased 63%. The study established that pharmacologic doses of vitamin E in Type II diabetes improve insulin's action and reduce free-radical activity (Paolisso 1993b).

Vascular endothelial dysfunction (an early marker of atherosclerosis) has been demonstrated in Type II diabetes mellitus. It appears hyperglycemia is particularly destructive to endothelial cells because it increases oxidative stress and impairs the activity of nitric oxide, the endothelial derived relaxing factor (Giugliano et al. 1995). Oxidative injury may be increased in diabetes mellitus because of a weakened defense due to reduced endogenous antioxidants (vitamin E and reduced glutathione). With compromised nitric oxide activity, diabetic-cardiovascular complications (smooth muscle proliferation, platelet activation/aggregation, and leukocyte adherence to the endothelium) are compounded.

Some of the strongest recent evidence of a vitamin E-diabetes benefit comes from researchers at the University of Texas Southwestern Medical Center in Dallas. Scientists found that vitamin E (1200 IU daily) reduced the risk of heart failure in 75 diabetics by curtailing vascular inflammation in the heart. Left unchecked, inflammation can cause cardiac vessels to swell, promoting cardiovascular disease. Dr. Sridevi Devaraj, assistant professor of pathology and lead researcher, termed the end results of the study very encouraging (Devaraj 2001).

Last, elevated levels of CRP, an inflammatory marker, have recently been found to predict the development of Type II diabetes. A newer finding relating to the functions of vitamin E is that high dose vitamin E lowers CRP. Administering 1200 IU of alpha-tocopherol (daily for 3 months) lowered CRP levels by 30%. CRP levels remained reduced 2 months postsupplementation. By preventing vascular inflammation, many of the complications arising from diabetes are overcome (Devaraj et al. 2000). A suggested vitamin E dosage is 400-1200 IU of vitamin E per day along with at least 200 mg of gamma tocopherol.

Vitamin K--may play a role in insulin's response to glucose

To evaluate the effects of vitamin K on pancreatic function, 25 healthy young male volunteers were evaluated as to plasma-glucose vitamin K levels at baseline and after an oral glucose load. Concurrently, a 1-week food diary estimated mean daily vitamin K intake.

Individuals consuming a vitamin K-rich diet tended to have higher blood vitamin K status then those participants who had less vitamin K in their diet (conclusion reached by examining an average of five blood samples). Fasting plasma glucose levels were not markedly different between the groups, showing about 86 mg/dL among all subjects. However, 30 minutes after a glucose load, the group with the higher vitamin K status had a plasma glucose level of 145 mg/dL; the group with the lower vitamin K levels presented with a plasma glucose level of 160 mg/dL. According to researchers, the results suggest that vitamin K may play an important role on the acute insulin response to glucose tolerance (Nishiike et al. 1999).

Elevated levels of C-reactive protein (CRP) and interleukin-6 (IL-6) have recently been found to predict the development of Type II diabetes mellitus. Since Vitamin K reduces levels of IL-6, it appears equally probable that vitamin K may also be effective in attenuating elevations in CRP. A suggested vitamin K dosage is 10 mg per day.

- Note: Persons on anticoagulant drugs such as Coumadin cannot take vitamin K.

Vitamin K-rich food sources and antagonists. Although friendly bacteria in the intestines synthesize the majority of vitamin K, the total requirement cannot be met by bacterial synthesis alone. Vitamin K-rich foodstuffs are liver and green leafy vegetables (especially broccoli, turnip greens, lettuce, and cabbage). Antibiotics increase the need for vitamin K, and vitamin E (doses less than 600 IU) antagonizes vitamin K activity.

WHY CONVENTIONAL TREATMENT FOR DIABETES CAN BE WORRISOME

- A Safer Oral Drug

By now, the reader is keenly aware that insulin in excess is dangerous. Too often, Type II diabetes patients are treated with insulin as the treatment of choice to control blood glucose levels. Most Type II diabetics have copious levels of insulin, at least before the disease becomes chronic and the pancreas exhausted. Injecting insulin into an already expanded insulin pool is a difficult rationale to

justify. Once the pancreas fails, insulin therapy becomes essential.

When Type II diabetes is diagnosed, patients are often treated with antidiabetic drugs that lower blood glucose by stimulating the pancreas to secrete more insulin. These insulin-stimulating agents are classified as sulfonylureas drugs. Conventional medicine also recommends dieting to control obesity (should it exist).

The problem with these conventional treatments is that the vast majority of diets fail to induce long-term weight control. While sulfonylureas drugs temporarily lower blood glucose, they saturate the blood with insulin and worsen the long-term prognosis. Examples of popular sulfonylureas medications and their mode of operation follow:

- Glimepiride (Amaryl) lowers blood glucose by stimulating the pancreas to produce more insulin.
- Glipizide (Glucatrol) controls diabetes by goading the pancreas into secreting more insulin.
- Glyburide (Micronase) controls blood glucose by stimulating the pancreas to produce more insulin and by helping insulin work more efficiently.

Drugs that continuously "whip" the pancreas into producing more insulin appear to be a shortsighted approach to treating the problem. This mechanism weakens the beta cells of the pancreas much quicker, plus the body must deal with the toxic effects of the additional insulin load. Chronically elevated levels of insulin raise the risk of degenerative disease (such as cancer and heart attack) and exacerbate the effect of diabetes.

When profiling many of the sulfonylureas drugs, the Physician's Desk Reference includes a perceptive comment: "It is possible that some oral diabetic drugs may lead to more heart problems than diet treatment alone, or diet plus insulin." (Recall that heart disease is regarded as the major complication arising from diabetes.)

Relying upon a sulfonylurea drug to correct a condition, often amendable through discipline, is asking more of a drug than we are asking of ourselves. If attempts at lifestyle modification fail to ameliorate hyperglycemia, oral agents may become necessary but are by no means desirable.

Too often the antidiabetic diet endorsed by orthodox physicians allows far too many carbohydrates to be effective. Recall that Dr. Steven Whiting, Ph.D., believes that chronic adherence to a high carbohydrate diet ensures that the diabetic individual will be a patient for life.

A Safer Oral Drug to Lower Blood Glucose Levels

Note: Because metformin (Glucophage) works from a different prospective in that it does not increase insulin production, it was selected for singular review.

The drug metformin (Glucophage) lowers the amount of sugar in the bloodstream by decreasing sugar production and absorption and by helping the body respond to its own insulin. Many American physicians now prescribe metformin as the first drug of choice. It was safely used in Europe decades before gaining FDA approval.

Metformin lowers fasting blood sugar levels in individuals at risk for Type II diabetes without causing a significant risk of becoming hypoglycemic. However, metformin-induced hypoglycemia is possible in older, weak, and undernourished people as well as those with kidney, liver, adrenal, or pituitary gland problems. If meals are missed, alcohol is consumed, or exercise becomes excessive, hypoglycemia could occur (PDR 1999).

Metformin increases insulin sensitivity, lowers serum insulin levels, and induces moderate weight loss. Metformin causes the number of insulin receptors in muscle and adipocyte cells (fat cells) to increase. Studies have demonstrated that metformin reduces fasting plasma glucose concentrations by 60-70 mg/dL in patients with Type II diabetes as well as HbA1c (Ketz 2001; Life Extension Foundation 2001).

Individuals who need support in maintaining diet-induced weight loss may find additional benefit from metformin therapy. Along with better weight

management, some individuals experience a decrease in the incidence of diabetes-associated infections. Some metformin users experience reductions in total and LDL cholesterol, free fatty acids, and two markers reflecting endothelial damage (tissue plasminogen activator antigen and von Willebrand factor) (Charles et al. 1999).

Metformin has better tolerability than many other antidiabetic prescription drugs, but individuals with congestive heart failure or kidney and liver disease are not candidates for metformin therapy. The restriction extends to include those who use alcohol to excess. A benchmark assessment of kidney function followed by an annual renal evaluation is essential (PDR 1999). Vitamin B12 levels should also be regularly checked because chronic use of metformin could cause a deficiency in both folic acid and vitamin B12, resulting in neurological impairment and disruption in homocysteine clearance.

A rare side effect associated with metformin is lactic acidosis, an accumulation of lactic acid in the bloodstream, resulting in a lower pH in muscles and serum (Klow et al. 2001). Almost all reported lactic acidosis cases occurred when metformin and a contrast medium were used in patients with preexisting poor renal function. Metformin should not be used for 2 days before or after having an x-ray procedure with an injectable contrast agent (radioactive iodine).

A number of food and drug interactions could occur with metformin therapy, but from natural medicine, high-dose niacin is the only dietary supplement that appears contraindicated. It is important to note that metformin (or any other antidiabetic drug) is only an aid to better glucose control, not a substitute for a good diet and a health-centered lifestyle with emphasis on exercise and stress reduction.

Many physicians report success when prescribing 500 mg of metformin 2-3 times a day to patients over 40, without extenuating health issues that preclude its usage.

SUMMARY

Diabetes mellitus is a disease characterized by disturbance in the body's use of glucose.

In Type I diabetes mellitus, the body does not make enough of the hormone insulin, which is needed for most tissues to be able to access and use glucose.

In Type II diabetes mellitus, the patient actually over produces insulin and experiences a systemic metabolic disorder that precludes the efficient utilization of glucose. Type II diabetes is the most commonly seen form of the disease. Everyone who is overweight is at risk of developing this disease.

In the later stages of Type II diabetes, the beta cells in the pancreas become dysfunctional and insulin-enhancement therapy becomes necessary. One of the objectives of this protocol is to keep Type II diabetics from progressing to the point where damaging insulin-enhancing therapies become necessary to suppress elevated blood glucose.

For the majority of Type II diabetics, the most important therapy to prevent or reverse the disease is to reduce excess body fat. The reader is asked to refer to the Obesity protocol to learn about novel methods of suppressing excess serum insulin, removing fat from storage and keeping new fat from accumulating in the body. Introducing physical activity into a sedentary lifestyle is also a critical therapeutic component.

The following list summarizes the nutrients profiled in the Therapeutic Section:

Alpha-lipoic acid protects LDL against oxidation and is beneficial in preventing and treating Syndrome X and diabetic complications such as neuropathy. As little as 250-500 mg daily of alpha-lipoic acid may be sufficient in healthy individuals. Diabetics usually take 250-500 mg of alpha-lipoic acid 3 times daily. For the last 30 years, German practitioners have used high doses of lipoic acid to improve insulin sensitivity and diabetic conditions.

- Carnosine interferes with the toxic glycation process, thereby preventing the formation of nonfunctioning structures in the body known as AGEs. Diabetics have greatly accelerated rates of glycation compared to nondiabetics. A suggested dosage is 1000 mg daily.
- Essential fatty acids protect the plasma membrane insulin receptors and reduce CRP.

Type II diabetics should supplement with at least 900 mg of GLA a day from borage oil, along with 500 mg of EPA and 1300 mg of DHA from fish oil. By using highly concentrated borage and fish oil supplements, this quantity of fatty acids (GLA, EPA, and DHA) can be obtained in 8 capsules.

- Carnitine improves blood glucose management and increases insulin sensitivity and glucose storage, essential for fat and carbohydrate metabolism. Deficiencies correlate with diabetic neuropathy. A suggested acetyl-L-carnitine dosage is 500-1000 mg twice daily.
- Chromium regulates blood glucose levels, fights insulin resistance, lowers HbA1c, aids in weight loss, and inhibits glycation. A suggested dosage is 200-600 mcg daily.
- DHEA deficiency is associated with a higher rate of insulin resistance and diabetes. A suggested dosage is 15-75 mg, taken early in the day (50 mg represents a typical daily dose). For a discussion relating to caveats surrounding DHEA supplementation, refer to the Therapeutic Section of this protocol.
- CLA aids weight loss and may improve insulin sensitivity. A suggested CLA daily dose is 3000-4000 mg (usually four to five 1000-mg (76%) CLA capsules).
- Magnesium lowers blood glucose levels, increases insulin sensitivity, and calms the SNS. Use at least 500 mg of elemental magnesium daily.
- Silymarin improves hepatic glucose control and reduces free-radical activity. A suggested dosage for Syndrome X patients (those not yet diagnosed with diabetes) is a supplement that provides 250 mg a day of silibinin and 60 mg of silymarin. Diabetic patients often take 2-3 of these silibinin/silymarin capsules each day.
- N-acetyl-L-cysteine (NAC) protects beta cells against free-radical destruction. A suggested dosage is 600 mg daily.
- CoQ10 enhances beta cell function and glycemic control and protects against heart disease. A suggested dosage is 100-300 mg a day.
- Vitamin C lowers blood glucose levels, inhibits glycation, prevents accumulation of sorbitol, strengthens capillaries, aids wound healing, and protects against free radicals. A suggested dosage is 1-3 grams daily in divided doses.
- Vitamin E reduces oxidative stress, enhances insulin sensitivity and glucose transport, and prevents complications arising from inflammation. Antidiabetic value has been observed using from 400-1200 IU of alpha tocopherol vitamin E daily along with a supplement that provides at least 200 mg of gamma tocopherol.
- Bilberry reduces blood glucose levels. A suggested dosage is 100-200 mg 3 times daily. (The bilberry extract should be standardized to contain 25% anthocyanidins.)
- Biotin aids in metabolism of macronutrients, enhances glucose utilization, and is beneficial in diabetic neuropathy. A suggested antidiabetic dosage is 8000-16,000 mcg daily.
- Vitamin K appears to play a role in insulin's response to glucose. Vitamin K is nontoxic at the recommended 10-mg daily dose.

A convenient way to obtain many of the nutrients listed is to take the following formulas:

- Life Extension Mix
- Life Extension Super Booster
- ChronoForte
- Super GLA/DHA

Some of the nutrients listed are to be taken individually.

Drug considerations:
In addition to diet modification, increased physical activity, and nutrient supplementation, Type II diabetics should consider low-dose aspirin (81 mg per day) to reduce their risk of heart attack and stroke.

The most effective prescription drug to treat many pathological mechanisms of Type II diabetes is metformin sold under the trade name Glucophage. Metformin is also available in generic form. Typical doses of metformin prescribed are 500 mg 2-3 times a day.

Aminoguanidine assists in controlling AGEs, a process that advances diabetic complications. Since aminoguanidine is not readily available, natural alternatives (alpha-lipoic acid, aspirin, carnosine, chromium, and vitamin C) become particularly attractive options.

Drugs to avoid:
If at all possible, avoid the sulfonylurea class of drugs that work by stimulating pancreatic secretion of insulin. While these drugs can lower elevated blood glucose for the short-term, they increase the risk of severe diabetic complications in the future. Insulin injections also increase the likelihood of diabetic complications. Persons with advanced diabetes may need insulin-enhancement therapy, but the objective is to control the disease state so that the body does not require huge amounts of insulin to maintain glycemic control.

- Note: Although fiber improves insulin sensitivity and reduces hyperinsulinemia, fiber should be slowly added to the diet, allowing time for digestive adjustments. Calculate the amount of fiber gained from foodstuffs and supplement to compensate for shortfalls. Successful trials used 50 grams of soluble and insoluble fibers a day. Monitor blood glucose levels closely to assess gains and to adjust either oral or injectable hypoglycemic agents. It is important that prediabetic and diabetic patients be evaluated regarding hemochromatosis, periodontal disease, and CRP levels. These conditions can hasten the onset of diabetes or worsen blood glucose control in confirmed cases; conversely, the correction of these anomalies can culminate in remarkable gains.

Refer to the Obesity protocol for critical information about suppressing excess serum insulin and reducing the percentage of body fat.

For more information

Contact the American Diabetes Association, (800) 232-3472.

Product availability

Alpha-lipoic acid, Life Extension Mix, Chronoforte, Life Extension Super Booster, bilberry extract, Biotin caps and powder, acetyl-L-carnitine, Super Carnosine, chromium capsules, CoQ10, conjugated linolenic acid, DHEA, Kyolic garlic, Fiber Food caps and powder, Super GLA/DHA, magnesium, NAC, Silibinin Plus, and vitamins C, E, and K are available by calling (407) 599-9600 or (800) 529-1163.

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