Type-I Diabetes: Prevention of the Disease And Its Complications

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Abstract

Type-I diabetes mellitus (IDDM) is a chronic degenerative disease with complications which can be devastating. There is an increasing body of research suggesting that prevention of IDDM by the avoidance of cow's milk and by the supplementation of niacinamide may be possible. This article will explore this research. The course the disease takes also may not be inevitable. Modification of diet and lifestyle factors as well as a comprehensive program of nutritional and botanical supplementation may help prevent the complications often encountered, such as neuropathy, retinopathy, nephropathy, micro- and macroangiopathy, and cataracts. This article will review the research on specific nutrients, botanicals, dietary and lifestyle factors, and their application in type-I diabetes.

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Introduction

Diabetes is defined as a disorder of carbohydrate metabolism caused by absence or deficiency of insulin, insulin resistance, or both, ultimately leading to hyperglycemia. Diabetes mellitus is typically classified into two main subtypes: type-I or insulin-dependent diabetes (IDDM), and type-II or non-insulin-dependent diabetes (NIDDM).

A more accurate way to differentiate the two would be to classify the insulin dependent diabetic as ketoacidosis-prone, and the non-insulin-dependent diabetic as ketoacidosis-resistant. Type-I and II would be differentiated on immunological-etiological grounds with type-I referring to an immune-mediated condition, whereas type-II is non-immune-mediated.[1] This classification would result in the potential for three groups — a type-I insulin-dependent group, a type-I non-insulin-dependent group, and a type-II non-insulin-dependent group. The type-I non-insulin-dependent group would encompass those non-obese diabetics for whom insulin is not yet required to prevent ketoacidosis but for whom islet cell antibodies are present in the blood. This group can be considered to have type-I insulin-dependent diabetes in evolution. The destruction of islet cells occurs gradually over time, so there is a delay in reaching the insulin dependency stage.

This article will focus on the prevention of type-I diabetes and its numerous complications. In the United States, the prevalence is estimated to be about 0.26 per cent of the population by age 20. The ratio of type-I:type-II varies depending upon the age group being assessed; the younger the age group, the greater the proportion of type-I diabetics. In general, diagnosis of all types is made by meeting one of two of the following criteria: (1) Fasting plasma glucose levels of 126 mg/dl or greater on at least two occasions or, (2) a plasma glucose level of 200 mg/dl or greater at two hours and on at least one other occasion during a 2-hour glucose tolerance test.

The Pathogenesis of Type-I Diabetes

It is believed that type-I diabetes has a genetic component which must be present for susceptibility to occur. Although the exact mechanism is unclear, transmission is believed to be autosomal dominant, recessive or mixed, although no mechanism has been proven. If a first-degree relative has IDDM, the child has a 5-10% chance of developing type-I diabetes.[1] It is believed that the susceptibility gene resides on the sixth chromosome, with the major alleles conferring risk being HLA-DR3, HLA-Dw3, HLA-DR4, HLA-Dw4, HLA-B8, and HLA-B15.

Secondly, an environmental insult, such as a virus, exposure to an allergen, or both, is believed to initiate the process in genetically susceptible individuals. This external influence precipitates an inflammatory response in the pancreas known as insulitis.[1] Activated T-lymphocytes infiltrate the islet cells in the pancreas. Macrophages and T-cells appear to be implicated in beta-cell destruction via localized release of cytokines.[2] Cytotoxic amounts of nitric oxide and reactive oxygen intermediates are also released, contributing to free radical damage to the beta cells. The initial steps in free-radical induced islet cell death involve breaks in DNA strands and the activation of the enzyme poly(ADP-ribose)polymerase (PARP). PARP is involved in DNA repair and consumes large amounts of NAD+ in the process. The depletion of intracellular NAD+ pools leads to islet cell death.[3] The inflammatory response is autoimmune mediated and takes place on the surface of the insulin-producing beta cells such that these cells are no longer recognized by the immune system. Antibodies against the beta cells are produced, resulting in their destruction and the clinical appearance of diabetes (see Table 1). This destruction is thought to occur slowly, over the course of several years in many cases.[1]

Some viruses seem to attack and destroy the beta cells directly, rather than initiating an autoimmune reaction.[4] A Venezuelan study conducted by Mijac et al reported a mumps infection prior to the onset of diabetes in 42.5% of subjects with IDDM vs. a 12.5% incidence in control subjects.[4] Elevated levels of Coxsackie virus IgM antibodies have been reported in patients with newly diagnosed type-I diabetes.[5] Large prospective studies have also found that exposure to enterovirus infections either *in utero* or during childhood may initiate beta-cell damage and subsequent type-I diabetes.[5] Other viral infections, including rubella and chicken pox, had no statistically significant correlation.[4] The effect of routine vaccinations as either a precipitating or preventive factor in diabetes has been alluded to by several researchers. Further study in this area seems indicated.

Table 1. The Pathogenesis of Type 1 Diabetes Mellitus. Adapted from Harrison's.[1]

Event	Agent or response
Genetic susceptibility	HLA-DR3, DR4, DW3, DW4, B8, B15
↓ Environmental event	Virus (?), Cow's milk protein (?)
↓ Insulitis	Infiltration of activated T lymphocytes
↓ Activation of autoimmunity	Self → nonself transition
↓ Immune attack on beta cells	Islet cell antibodies, cell mediated immunity
↓ Diabetes mellitus	>90% beta cells destroyed (alpha cells unopposed)

The Role of Alternative Medicine in Type-I Diabetes

There is increasing evidence that with appropriate genetic screening measures type-I diabetes may be prevented or halted if caught before total destruction of the beta cells occurs. This will be discussed in further detail below. Unlike type-II diabetes, which may be controlled without medication, alternative therapies are used as adjuncts to exogenous insulin in type-I diabetes. Nutritional supplements, botanicals, diet, and lifestyle considerations have application in decreasing insulin requirements and helping to maintain more normal blood glucose levels. In addition, they may prevent the onset of complications of hyperglycemia, including retinopathy, nephropathy, neuropathy and macro- and microangiopathy.

Prevention of Diabetes

There is increasing evidence that type-I diabetes can be prevented. This involves intense screening of high-risk populations. Since only 10% of cases are familial, screening of all people at risk for type-I diabetes is impossible without screening the entire population. Evaluations involve both immunological and genetic screening. Markers associated with future onset of diabetes, including islet cell antibodies (ICA), glutamic acid decarboxylase antibodies (GAD), antibodies against protein tyrosine phosphatase/IA2 and antibodies against the 37/40 K antigen, appear in the circulation years before clinical onset of disease.[2]

Knowledge of the pathogenesis of IDDM and prevention studies suggest that progression to disease in antibody-positive individuals may not be inevitable; that the autoimmune processes directed against the beta cells may prove vulnerable to intervention. Some of the research on prevention has centered around the use of immuno-suppressive therapy with the use of medications such as deflazacort, cyclosporin A and azathioprine. Use of these has not resulted in significant long-term improvement in beta-cell functioning, but only in 6-12 month remissions.[5,6] Other immunosuppressive and immunomodulating drugs are in various stages of investigation.[5]

Other strategies which seem to hold some promise include intensive insulin therapy[7] and tolerance induction with injections of Bacille Calmette-Guerin (BCG) or GAD. Neither BCG nor GAD injections have resulted in prevention of diabetes in humans;[5] however, insulin therapy holds some promise. When insulin was given to prediabetics, first-degree relatives who were in late-stage prediabetes and expected to overtly manifest the disease within three years, the five who accepted the therapy remained diabetes free for 5.8 years. One has subsequently developed diabetes. The seven who refused insulin treatment were followed and all developed diabetes, six of them within three years.[5] The treatment involved a five-day course of intensive IV insulin every nine months, plus daily low-dose subcutaneous injections.

Treatment of newly diagnosed adolescent diabetics with conventional insulin therapy vs. conventional plus 14-day intensive continuous IV insulin therapy yielded promising results by improving beta-cell function for one year.[8] It is postulated the insulin may act as an antigen, altering the autoimmune attack on the beta cells by repeated immunization. There is also a beta-cell rest hypothesis which suggests exogenous insulin gives the beta cells a rest, preserving their ability to secrete endogenous insulin. *In vitro* it has been found that activated beta cells are more susceptible to immune attack by cytokines than are beta cells at rest.[5] Vaccinations against potential viral triggers are also being explored.

The cow's milk connection: Cow's milk has been implicated as a possible trigger of the autoimmune response, resulting in antibodies to and subsequent destruction of

beta cells in genetically susceptible people. Karjalainen et al, in their 1992 study published in the *New England Journal of Medicine*, postulated on the specific mechanisms involved.[9] Comparing a group of 142 Finnish children with newly diagnosed IDDM with 79 healthy children and 300 adult blood donors, they found elevated IgG antibodies to bovine serum albumen (BSA) in all diabetic patients. While they found low levels of this antibody in many healthy children, the concentrations in the diabetic patients were an average of seven times higher.[9] They further identified a specific 17-amino-acid peptide (ABBOS) on the BSA molecule as the antigenic portion.[9] This portion differs from the sequence in human, rat or mouse albumins. It is believed the antibodies cross-react with a surface antigen on the beta cell called p69. Infectious disease, most likely viral in nature, stimulates release of interferon gamma. The interferon in turn is responsible for induction of the beta-cell surface antigen. Thus, it appears cow's milk protein, in conjunction with viral exposure, may be implicated in the etiology of IDDM. They found only low concentrations of IgG antibodies to two other cow's milk proteins, casein and ß-lactoglobulin. The concentrations of these proteins were similar in both the diabetic and non-diabetic groups, implicating bovine serum albumin but not others.

A French study found a similar correlation between IgG anti-BSA antibodies and IDDM. Levy-Marchal et al found elevated anti-BSA antibodies in 74.4% of newly diagnosed diabetics, in 20% of ICA positive non-diabetics, and in only 5.5% of controls.[10] Cavallo et al, on the other hand, found a connection between ß-casein and IDDM. They found specific proliferation of T-lymphocytes with bovine ß-casein in 51% (24 of 47) of patients with diabetes compared to 2.7% (1 of 36) of healthy subjects, demonstrating a positive response to ß-casein.[11] To further the inconsistency, Saukkonen et al, in a Hungarian study, found a correlation between high levels of IgM antibodies to both bovine serum albumin and ß-lactoglobulin and IDDM. The levels of IgG and IgA antibodies were similar in the diabetic and non-diabetic groups.[12]

In a previous study in Finland, Saukkonen et al found patients with diabetes to have significantly higher levels of IgA and IgG antibodies to BSA, while levels of IgA antibodies to ovalbumin were not significantly different between diabetics and controls, and IgG levels were higher in controls.[13] Norris et al, in their Diabetes Autoimmunity Study in the Young, found no correlation between beta-cell autoimmunity (BCA) and early exposure to cow's-milk protein. Two hundred fifty-three children were screened for BCA, which was defined as elevated levels of insulin autoantibody, glutamic acid decarboxylase autoantibody, or insulinoma-associated islet tyrosine phosphatase autoantibody above the 99th percentile of 198 normal subjects. There were no differences between cases and controls in regard to exposure to cow's-milk protein before the third or sixth month of life.[14] It should be noted, however, that although 253 children were screened for BCA, only a small group of 18 were antibody-positive. Similarly, Mijac et al found no correlation between early exposure to cow's milk and IDDM.[4] Perez-Bravo et al found a correlation between early (before three months of age) exposure to cow's milk and other solid foods versus exclusive breast-feeding and IDDM.[15] Eighty diabetic children were compared with 85 non-diabetic children. Fewer children in the diabetic group were exclusively breast-fed, and exposure to cow's milk occurred earlier in the diabetic group.[15] Vaarala et al found an enhanced immune response to ß-lactoglobulin in 55% (22 of 40) of newly diagnosed type-I diabetics compared with 22% (7 of 32) of healthy children.[16]

The Childhood Diabetes in Finland Study Group examined siblings of diabetics and found cow's milk proteins to be elevated

in those who also tested positive for islet cell antibodies.[17] The researchers postulated an enhanced transfer of antigens across the gut barrier in these subjects. In summary, many researchers have found statistically significant correlations between antibodies to cow's milk protein, particularly to bovine serum albumin[9,12,13,17] and the incidence of IDDM. The avoidance of cow's milk as a substitute for breast milk, at least in the first six months of life, seems warranted as a prevention for type-I diabetes.

Beta-cell preservation by nicotinamide: Nicotinamide (niacinamide), a form of vitamin B3, has the capability *in vitro* of interrupting the pathogenetic mechanisms of IDDM. Animal studies have yielded significant beta-cell protection from niacinamide. Nitric oxide is believed to be a potent mediator in the pathogenesis of type-I diabetes as it exerts cytotoxic and inhibitory effects on pancreatic beta cells. Using isolated rat islet cells, Akabane et al found that high concentrations of niacinamide (20mM) but not low (5mM) offered beta-cell protection.[18] Researchers used a casein-free diet plus nicotinamide in mice to prevent insulitis, a precursor to the development of diabetes. They further found that when females were fed the casein-free, soy-based diet at conception, rather than at day 21, a greater suppression of insulitis resulted, indicating that the maternal diet during gestation may be of importance in preventing diabetes in the offspring.[19]

Since 1987, several studies have evaluated nicotinamide's ability to prevent beta-cell destruction in patients newly diagnosed with type-I diabetes. Niacinamide's mechanisms of action include inhibiting the enzyme poly (ADP-ribose) polymerase (PARP), preventing depletion of intracellular NAD^+, and quenching of free radicals.[9,20] PARP is responsible for cleaving NAD^+, causing NAD^+ levels in the cytosol to fall to zero. As mentioned previously, low intracellular NAD^+ levels contribute to the death of islet cells.

Pozzillo et al conducted a meta-analysis of 10 different controlled trials of nicotinamide on newly diagnosed IDDM patients. Parameters for evaluating glucose control were C-peptide, glycosylated hemoglobin (HbA1c), and insulin requirements. C-peptide is that portion of proinsulin which remains after insulin is cleaved from the molecule. It parallels in a 1:1 ratio the levels of endogenous insulin. Exogenous insulin injections do not result in increased levels of C-peptide. One year after diagnosis, C-peptide was significantly higher in nicotinamide-treated patients; an average of 0.73 ng/ml vs 0.32 ng/ml in the placebo group. No differences in insulin requirement or HbA1c were noted.[21] The only reported side effects included skin rash, transient elevation of serum transaminase, and recurrent hypoglycemia, each in two patients.

A double-blind trial on 56 newly diagnosed diabetics, using niacinamide and three to four insulin injections a day versus placebo and insulin, yielded mixed results. There were no significant differences between the niacinamide and placebo groups for insulin requirement, glycosylated hemoglobin or C-peptide in children under 15 years of age. When age at diagnosis was taken into account, patients over age 15 demonstrated significantly higher C-peptide secretion.[22]

In another study, Pozzilli et al studied 80 patients. Twenty-seven were treated with niacinamide, 25 with niacinamide plus cyclosporin, and 28 served as controls. They were treated for 12 months; then treatment was discontinued and they were followed for another 12 months. Insulin requirements doubled 12 months after discontinuing the nicotinamide or nicotinamide plus cyclosporin, becoming identical to that of controls.[7] Furthermore, glycosylated hemoglobin values were similar to controls one year after treatment. It appears that beta-cell function deteriorated after discontinuing the therapy.

In a small clinical trial conducted by Taboga et al, recently diagnosed subjects

received insulin plus nicotinamide, three grams daily (n=11) or insulin alone (n=10) for two years. Insulin requirements, bimonthly HbA1c, and half-yearly C-peptide evaluations were recorded. No significant differences were observed between the two groups.[23]

Results of the use of nicotinamide in early-onset type-I diabetes have been equivocal. While niacinamide appears to help prevent beta-cell death, it does not intervene in the inflammatory process. Vague et al reported that niacinamide extended the remission or honeymoon phase often seen after initial diagnosis, during which time the patient's insulin requirement decreases or temporarily disappears. However, the patients reverted to dependence on insulin within one year.[24] This is similar to the effect of immunosuppressive drugs such as cyclosporin-A.[5]

With the advent of screening methods capable of predicting which individuals are at high risk for developing IDDM, it may be possible to employ preventive measures prior to the onset of disease. Screening involves testing for islet cell antibodies in first-degree relatives (parent, child, sibling) of individuals with IDDM. First-degree relatives have a 10% chance of developing IDDM within five years. The risk increases to 35% when ICA titers are greater than 20 Juvenile Diabetes Foundation units. The presence of glutamic acid decarboxylase antibodies carries a risk of 17%, and if both ICA and GAD antibodies are present the combined risk is greater than 90%.[25]

A population-based diabetes prevention trial was conducted with a group of 20,195 New Zealand school children. Of these, 185 had ICAs, meeting the criteria for a niacinamide prevention trial. The average follow-up time was 7.1 years. Diabetes incidence of untested controls was 16.07 (12.4-20.5 95% CI)/100,000 person years at risk, while the incidence in the tested group, which was niacinamide treated when antibody positive, was 7.14 (3.1-14.1 95% CI)/100,000 person years. Another group of 13,463 individuals who were offered testing but refused had a diabetes incidence of 18.48 (10.1-31.0 95% CI). The tested and treated group had 41% the incidence of diabetes of the other two groups combined. It was concluded that, although the size of the effect had a wide confidence interval, the nicotinamide had a protective effect for the development of IDDM.[26]

A word of caution must be interjected, however; niacin has been known to cause insulin resistance in normal subjects. Greenbaum et al designed a study to determine if niacinamide might do the same. The study involved eight islet-cell-antibody-positive relatives of type-I diabetics. They were given two grams of niacinamide daily for two weeks. Measurements of insulin sensitivity, insulin release, glucose effectiveness, and the constant for glucose disappearance (Kg) were taken at baseline, at the end of two weeks of therapy and after subjects had been off therapy for at least two weeks. Nicotinamide administration caused a 23.6% decrease in insulin sensitivity (P=0.02).[27] Their conclusion was, "the use of nicotinamide in subjects who are at risk of developing IDDM may be complicated by the drug's effects on insulin sensitivity." This merits a larger-scale investigation. Further clinical trials should have at least one subgroup being tested for insulin sensitivity and insulin secretion.

Other preventive measures: Mathieu et al found a vitamin D3 analog (1 alpha-25-(OH)2-20-epi-22-oxa-24,26,27-trishomovitamin D), in doses low enough to prevent hypercalcemia and bone demineralization, to prevent diabetes in mice. The suggested mechanism of action was the restoration of suppresser cell activity.[28] Hypersecretion of insulin increases the likelihood of incidence of both type-I and II diabetes; inhibition of secretion helps prevent diabetes. Both vanadium and zinc may act like insulin and

decrease the hypersecretion of insulin, ultimately reducing the risk of developing diabetes.[29] Supplementation of vanadium as well as zinc also helps ensure that beta cells do not lose too much zinc during periods of stress.[29] There is evidence that low levels of zinc in drinking water may predispose toward IDDM.[30]

The future of prevention: Three large clinical trials are planned or underway to determine whether early intervention can prevent IDDM in persons at risk but who have not yet demonstrated clinical signs of disease. In the Cow's Milk Avoidance Trial, infants who have siblings with IDDM are randomized to receive either a cow's-milk-based formula or a non-antigenic protein formula. The Diabetes Prevention Trial-Type-I is randomly assigning people with a greater than 50% probability of developing IDDM to receive insulin injections or observation; subjects at intermediate risk will receive either oral insulin or placebo. In the third trial, the European Nicotinamide Diabetes Intervention Trial, subjects at risk either receive nicotinamide or placebo.[31] Depending upon the results of these trials, large-scale screening of children for IDDM risk factors may be warranted.

Preventing the Complications of Diabetes — Neuropathy, Nephro-pathy, Retinopathy, Microangiopathy, Cataracts — With Single Nutrient Intervention.

There is a plethora of information on the use of nutritional supplements and botanicals to manage blood sugar and prevent diabetic complications. The remainder of this article will examine many of the single nutrients and botanicals that have application in a treatment protocol for type-I diabetes. Some of these substances have been well-researched, while important research remains to be done on many of them.

Nutrients may be used to correct deficiencies which tend to prevail in patients with type-I diabetes. In addition, they may be used in pharmacological dosages to affect a particular metabolic change. The mechanisms of prevention involve inhibition of non-enzymatic protein glycation, inhibition of sorbitol pathway activity by aldose reductase inhibitors, prevention of hypoxia by vasodilators, inhibition of increased vascular permeability, and prevention of oxidative stress and free radical generation.[32,33] For nutrient effects at a glance, see Table 2.

B vitamins: Levels of B vitamins, particularly pyridoxine, tend to be low or marginal in diabetics.[34-37] Thiamine (B1)[36] and cobalamin (B12)[37] are occasionally low, while the metabolism of riboflavin (B2) appears to be abnormal.[36,38] Due to abnormal metabolism of riboflavin, giving the activated form, riboflavin-5-phosphate, may be the most effective method of supplementation.

Pyridoxine levels appear to be low, particularly in patients with neuropathy.[39] The use of B6 for the treatment of diabetic neuropathy has met with mixed results. Jones et al reported on the use of 50 mg pyridoxine three times daily in 10 patients with diabetic neuropathy and "signs of pyridoxine deficiency." Seven of 10 patients had improvement in pain and paresthesias within 10 days, followed by a recurrence of symptoms within three weeks of discontinuing treatment. This relapse abated when treatment was resumed.[40]

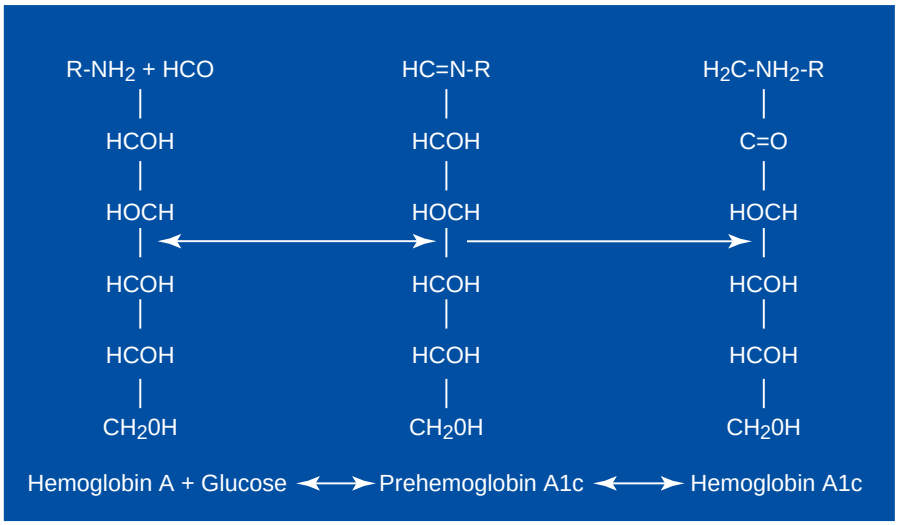
A study by Levin et al found no significant effect from the use of B6 on 18 patients with diabetic neuropathy. After four months of treatment, six of nine treated with 50 mg three times daily and four of nine in the placebo group reported significant relief. There was no difference between the two groups with regard to motor nerve conduction velocity.[41]

In the Jones study, all patients exhibited some pyridoxine deficiency, while in the Levin study only one patient had a low plasma pyridoxal phosphate level at the beginning of

Table 2. Specific Nutrient Effects On Type 1 Diabetes

NUTRIENT	FUNCTION	DOSAGE RANGE
NIACINAMIDE	Protects beta-cells from destruction	1-3 grams/day
PYRIDOXINE	Correct a deficiency; neuropathy; retinopathy	50-200 mg/day
RIBOFLAVIN	Diabetics have abnormal B2 metabolism; use R5P	50-100 mg/day
THIAMINE	Correct a possible deficiency; neuropathy	50-100 mg/day
BIOTIN	Correct deficiency of abnormal metabolism; neuropathy	8-16 mg/day
B12	Correct a deficiency; neuropathy; lower homocysteine	100-1000 mcg/day
FOLATE	Lower homocysteine levels to prevent retinopathy and nephropathy	1 mg/day
VITAMIN C	Prevents protein glycosylation; antioxidant; Aldose reductase inhibitor	1-10 grams/day
VITAMIN E	Prevents protein glycosylation; antioxidant; Reduces LDL oxidation	400-800 IU/day
QUERCETIN/ QUERCETRIN	Aldose reductase inhibitors	400-500 mg tid
NARINGIN	Aldose reductase inhibitor	400-500 mg tid
HESPERIDIN	Aldose reductase inhibitor	400-500 mg tid
INOSITOL	Restores intracellular inositol; neuropathy	500 mg bid-tid
SELENIUM	Antioxidant	200-400 mcg/day
CHROMIUM	Enhance insulin binding; reduce insulin requirement	500-1000 mcg/day
VANADYL SULFATE	Has insulin-like effects -- decreases serum glucose	5 mg tid
MAGNESIUM	Restore levels typically low in diabetics	500 mg/day
ZINC	May exert insulin-like effects; protects beta-cells	30 mg/day/2 mgCu
MANGANESE	Corrects a deficiency	10-50 mg/day
EFAs	Metabolism impaired in diabetics; vasodilation improves nerve conduction; microangiopathy; neuropathy	1-3 g/day
LIPOIC ACID	Prevents protein glycosylation; antioxidant; Stimulates glucose uptake by muscle cells	300-600 mg/day
ACETYL-L-CARNITINE	Restores myo-inositol levels; antioxidant; neuropathy; retinopathy	500-1000 mg tid
TAURINE	Reduces abnormal platelet aggregation; restores depressed levels	500 mg tid
PAK	Lowers glucose levels in DM; helps prevent lactic acidosis	2-3 g/day
COENZYME Q	Group of enzymes low in diabetics; neuropathy	30-100 mg/day
PANTETHINE	Lowers blood lipids in diabetics; neuropathy	200-300 mg tid

Figure 1. Glycosylation of Hemoglobin



the study. It may be that pyridoxine is helpful for the treatment of neuropathy only in those patients who are deficient. Since both studies were on small populations, study of a larger population seems warranted.

Stanley Mirscky, MD, former president of the New York affiliate of the American Diabetes Association (ADA), in his book, *Diabetes: Controlling it the Easy Way* , makes the clinical observation that 80% of diabetics with sensory neuropathy improved with thiamine supplementation. Stracke et al reported on a 12-week study of 24 diabetics with polyneuropathy who were treated with benfotiamine (a lipid soluble derivative of thiamine with high bioavailability), B6 and B12. Significant improvement in nerve conduction velocity as well as a trend toward improved vibrational perception were observed.[42] A longer term observation of nine patients for nine months supported these results. Several rat and human studies have demonstrated the possible benefit of B12 for the treatment of neuropathy.[43-45]

Biotin was given for 1-2 years to three diabetic patients suffering from peripheral neuropathy. There was marked improvement in laboratory and clinical findings within eight weeks. This suggests a possible deficiency or disordered metabolism of biotin in the pathogenesis of diabetic neuropathy.[46] A retrospective study of 18 diabetic patients over a period of from eight months to 28 years found a significant absence of retinopathy in B6-treated individuals.[35] Because of the low toxicity of the B vitamins, it would seem prudent to have all diabetic patients on a B-complex supplement.

Magnesium is necessary for the conversion of pyridoxine to its active form, pyridoxal 5'-phosphate (PLP). Since many diabetics are deficient in this important mineral,[47,48] supplementation with PLP may provide the most benefit for diabetics. Since, in the above-cited studies, neither magnesium nor the activated form of B6 were used, the equivocal results may have been, at least in part, due to faulty conversion of pyridoxine.

Glycosylation and Antioxidants: It is believed that one of the mechanisms responsible for secondary complications of diabetes involves non-enzymatic glycosylation of proteins by glucose auto-oxidation.[49] It is the glycosylation of hemoglobin which offers a marker of long term blood sugar control (see Figure 1). Glycosylated proteins generate free radicals, causing oxidative stress and tissue damage. When a cell suffers oxidative injury, cytosol NAD^+ and ATP levels fall. Unless intracellular NAD^+ levels can be restored, cell death will ensue. Antioxidants such as vitamins C and E have been shown to reduce protein glycosylation both *in vivo* and *in vitro.*[49,50] They also act as scavengers of free radicals generated by the glycosylated proteins.[49] Davie et al supplemented 12 non-diabetic subjects with one gram daily of ascorbic acid and demonstrated significant decreases of

glycosylated hemoglobin (18% decrease) and glycosylated albumin (33% decrease) over a three-month period.[50] In contrast, Weykamp et al found no decrease is glycosylated hemoglobin when healthy volunteers were supplemented with 750 mg or 1500 mg of ascorbic acid daily for 12 weeks.[51,52] Jain et al found a significant reduction in glycosylated hemoglobin as well as a lowering of triglycerides in 35 type-I diabetics supplemented with 100 IU dl-alpha-tocopherol for three months.[53]

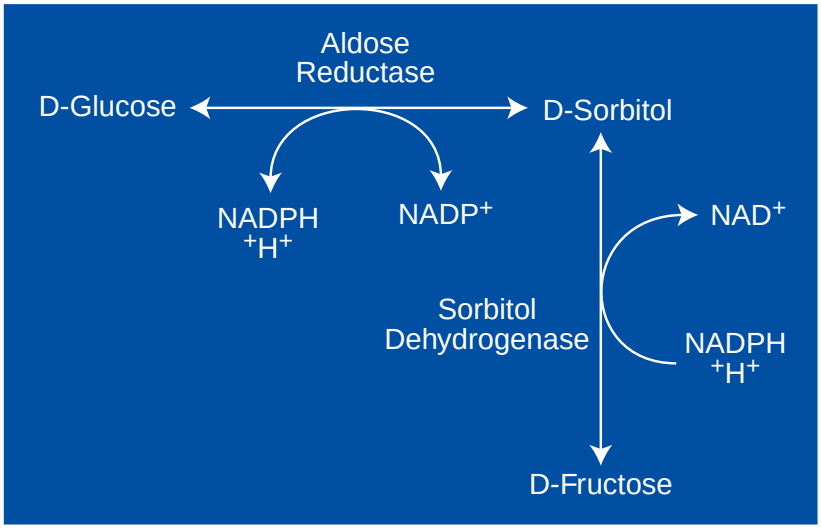
Glutathione levels appear to be subnormal in the retinas of diabetics. Ascorbic acid and alpha-tocopherol, fed to diabetic rats, significantly increased glutathione levels in the retina.[54] Carboxymethyl lysine (CML) is a byproduct of oxidation of glycated proteins and is used as a marker for oxidative stress. Formation of CML has been found to decrease with various antioxidants, particularly vitamin E, as well as the more recently researched potent antioxidant, lipoic acid.[55]

Preventing oxidative damage: Antioxidants have an impact on diabetic complications via mechanisms other than prevention of protein glycosylation. Cardiovascular complications of diabetes are, in part, due to small vessel damage by oxidized LDL. Fuller et al found vitamin E, at a dosage of 1200 IU daily in the form of tocopheryl acetate, elicited significant reductions in LDL oxidation, but had no significant effect on lowering plasma glycosylated protein or glycosylated hemoglobin.[51] Kuznetsov et al found normalization of lipid peroxidation in hypertensive diabetics with alpha-tocopherol acetate.[56] Douilet et al found a significant protective effect of vitamin E and selenium on the kidneys of diabetic rats. Plasma lipid peroxides, glucose, and TGs were also decreased.[57] Cary and McCarty report on 19/20 diabetic patients who had either improvement or no progression of retinopathy when supplemented with 500 mcg selenium, 800 IU vitamin E, 10,000 IU vitamin A, and one gram vitamin C daily for several years.[58] Ongoing research is underway at this time. The MICRO-HOPE study is examining the effect of an ACE inhibitor and vitamin E on the progression of renal and cardiovascular disease in 3,657 diabetics.[59]

Lipoic acid (thioctic acid) is a physiological constituent of cell membranes and acts as a potent antioxidant, both within the cell membrane and in the cytosol. Lipoic acid or its reduced form, dihydrolipoic acid, reacts with reactive oxygen species including superoxide radicals, singlet oxygen, hydroxyl radicals, peroxyl radicals, and hypochlorous acid.[60] Dihydrolipoic acid was found to protect rat islet cells from the destructive effects of reactive oxygen species and to suppress nitric oxide production, substances released by macrophages during insulitis.[3] Lipoic acid has been used extensively in Germany for the treatment of diabetic neuropathy.[61] Lipid peroxidation is increased in experimental diabetic neuropathy. *In vitro* studies by Nickander et al found that lipoic acid significantly decreased lipid peroxidation of nerve tissue.[62] Lipoic acid stimulates glucose uptake by muscle cells in both rat and human studies in a manner comparable to insulin.[61] Kahler et al divided a group of 80 diabetics suffering from complications into four groups. One group served as the control group, one received lipoic acid 600 mg daily, one 1200 IU d-alpha-tocopherol, and one 100 mcg selenium. All groups treated with antioxidants showed significant diminution of urinary albumin and thiobarbituric acid (a reactive species and indicator of oxidative processes). Neuropathy symptoms of thermal and vibratory sensitivities were also significantly improved.[63]

The Sorbitol Pathway - The road less traveled (or so we hope): The sorbitol pathway converts glucose to sorbitol and then to fructose. It is especially active in diabetics as glucose rises in tissues that are not insulin

Figure 2. The Sorbitol Pathway



sensitive — the lens of the eye, renal glomeruli, and peripheral nerves. Excess glucose passively diffuses into cells and is reduced to sorbitol by NADPH with the help of the enzyme aldose reductase. In the presence of NAD^+ sorbitol is oxidized to fructose, catalyzed by the enzyme sorbitol dehydrogenase (see Figure 2). Since sorbitol does not diffuse passively through cell membranes, it accumulates, along with some fructose, within the cell, thus resulting in cell damage. This elevation of sorbitol also results in a drop in myo-inositol (inositol) levels.[64] These events are believed to play a primary role in the development of diabetic complications such as peripheral neuropathy, cataracts and nephropathy. Animal and *in vitro* studies have demonstrated the efficacy of aldose reductase inhibitors (ARIs) in the prevention of diabetic cataracts, retinopathy and nephropathy, and in early-stage diabetic neuropathy.[3]

While there are numerous drugs that inhibit aldose reductase, there are also a number of single nutrient substances which do the same. Vitamin C has been found, *in vitro* [65] and *in vivo* [66,67] to inhibit aldose reductase in RBC erythrocytes. Vinson et al gave eight diabetic subjects 2000 mg daily of ascorbic acid for three weeks, and erythrocyte sorbitol levels decreased by 44.5%. In an *in vitro* test, they found 500 mg ascorbate alone decreased erythrocyte sorbitol by 12.6% vs a 27.2% decrease by ascorbate in a citrus fruit medium.[66]

Cunningham et al found similar results with lower doses of vitamin C. Comparing IDDM adults with non-diabetics, 100-600 mg ascorbate was given daily for 58 days. Blood glucose control in the diabetics was moderate to poor. Initially high RBC sorbitol levels (doubled in the diabetic patients) were brought to normal in 30 days with vitamin C supplementation.[67]

Various flavonoid compounds, including quercetin, quercetrin, naringin, and hesperidin have also been found to be aldose reductase inhibitors.[68,69] ARIs have been found to prevent diabetic cataracts.[70] The bioflavonoid quercetin has been found, *in vitro* to inhibit sorbitol accumulation in human lenses.[71] Studies on diabetic animals have found another bioflavonoid, quercitrin, to impede the course of cataract formation.[72,73] A rat study did not yield positive results with the use of a quercetin for cataract prevention.[74] Refractive changes in the direction of hyperopia in diabetics have also been attributed to sorbitol accumulation in the lens. Varma et al found flavonoids to significantly attenuate this process in diabetic rabbits.[75] Animal studies indicate quercetin's application in diabetes may also include normalization of glycemia, reduction of total cholesterol and LDL,[76] and prevention of oxidation of LDL.[77]

Lipoic acid has also been noted as an aldose reductase inhibitor. Transition metals may be involved in activating the sorbitol pathway; ARIs, including lipoic acid, act as metal chelating antioxidants.[78] A constituent of licorice root (*Glycyrrhiza glabra*) has been found to exhibit potent aldose reductase inhibition.[79,80] The component, isoliquiritigenin, was found to decrease sorbitol levels in the sciatic

nerve of diabetic rats. This same study demonstrated a marked decrease in production of prostacyclin (PGI2) by isoliquiritigenin.[79] This could have implications for mediation of not only diabetic neuropathy but also cardiovascular complications.

As previously mentioned, elevation of sorbitol within a cell results in a drop in inositol levels. Untreated diabetics also appear to have altered inositol metabolism. Six diabetic patients, before and after insulin therapy, were compared with 10 non-diabetics. The dietary inositol intake and fecal inositol excretion were similar in both groups. However, the untreated diabetics exhibited a 10-fold increase in urinary inositol. Insulin restored the urinary inositol excretion to normal. Plasma inositol levels were high in untreated diabetics due to impaired intracellular transport. This too was corrected by insulin therapy.[81]

Lower intracellular inositol levels are thought to affect the development of neuropathy in several ways. Experiments with streptozotocin (STZ)-induced diabetic rats indicate axonal transport of the enzyme choline acetyltransferase is reduced in the sciatic nerve. When the lowered inositol content of the nerve cells was reversed by aldose reductase inhibitors or dietary inositol, the defective enzyme transport was reversed.[82]

Another mechanism suggested by animal studies is that the slowing of nerve conduction, a hallmark of diabetic neuropathy, is caused by a low myo-inositol-related defect in neuronal sodium-potassium adenosine triphosphatase (Na(+)-K(+)ATPase).[83,84] This enzyme is responsible for generating action potentials across the nerve cell membrane, allowing for nerve impulse conduction. Decreased Na(+)-K(+)ATPase activity in diabetic rat nerve is normalized by ARIs or dietary inositol.[85] Salway et al supplemented seven diabetic patients with 500 mg inositol twice daily for two weeks. The amplitude of evoked action potentials in the sural, median, and popliteal nerves was increased by an average of 160%, 76%, and 40%, respectively, without an increase in conduction velocities during this short time period.[86] Sima et al fed normal rats a diet high in L-fucose, a competitive inhibitor of myo-inositol. After 24 weeks, nerve inositol levels and Na(+)-K(+) ATPase activity decreased significantly. The result was axonal atrophy, paranodal swelling and paranodal demyelination. Dietary inositol supplementation prevented these structural changes and increased nodal remyelination.[87]

Green et al concluded the reversible paranodal swelling seen in rat peripheral nerves was due to an inositol-related defect in (Na+)-(K+)ATPase rather than the osmotic effect of sorbitol accumulation.[88] Inman et al addressed the hypothesis that diminished renal arteriolar reactivity to angiotensin II and norepinephrine (NE) in diabetes is the result of inadequate inositol incorporation into membrane phospholipids. The results of their rat study indicate improved reactivity to angiotensin II but not to NE in diabetic rats fed a myo-inositol-enriched diet.[89] D-chiroinositol but not myo-inositol significantly lowered plasma glucose levels in STZ-treated diabetic rats, normal rats fed a glucose load, and insulin-resistant monkeys.[90]

Capillary basement membrane (CBM) thickening in retinal and glomerular capillaries has been implicated in the pathogenesis of diabetic retinopathy and nephropathy, respectively. Tilton et al, in a study of diabetic rats, found no improvement in CBM thickening in retinal capillaries of rats fed an inositol-enriched diet. The inositol-fed rats had an increase in glomerular CBM thickening over controls.[91] On the other hand, Chakrabarti and Sima found a diminution in retinal CBM width in rats supplemented with inositol, although other structural changes were not affected.[92]

Mineral supplementation in type-I diabetes: Chromium is necessary for normal carbohydrate and lipid metabolism. It is believed to enhance insulin binding to cell receptors. Two-hundred mcg per day elemental

chromium, from chromium picolinate, reduced the insulin requirement in 71.6% of 58 adults with type-I diabetes, as compared to 74% of type-II diabetics.[93] Another study comparing the same form and dose on type I and type-II diabetics found a greater difference between the effects on type-II and type I. Requirements for insulin or other hypoglycemic agents were reduced in 57.2% of type-II diabetics compared to 33.6% of type I diabetics.[94] Injections of glucose tolerance factor (of which chromium is a constituent) to STZ-diabetic rats, with no exogenous insulin, reduced blood glucose and free fatty acids within two hours.[95]

Vanadium has been found to have important application in the treatment of IDDM. Bosia et al report on vanadium's protective effect on diabetic cataracts and nephropathy in STZ-diabetic rats.[96] The protection was improved slightly with the addition of vitamin E. Vanadium has insulin-like effects and is currently being considered for oral therapy. It also reduces gluconeogenesis and increases glycogen deposition.[97] Vanadium salts induce sustained falls in blood glucose in diabetic rodents.[98] Insulin appears to affect the metabolism of vanadium. The half-life of vanadium varies among organs with insulin-sensitive tissue, such as liver and fat, which metabolize vanadium more quickly.[99] Toxicity studies on rats concluded vanadyl sulfate, in doses necessary to cause euglycemia, was not toxic after one year of administration; however, vanadium may be retained in organs for months after administration has ended.[100]

IDDM patients tend to be low in serum magnesium. A group of 71 people who had had diabetes for 10-20 years were divided into two subgroups depending on severity of retinopathy. Hypomagnesemia was most pronounced in patients with the most severe retinopathy.[47] IDDM has been found to cause altered electrolyte metabolism and derangements in the parathyroid hormone-vitamin D axis, resulting in lower ionized calcium, magnesium, parathyroid hormone (PTH), calcitriol, and osteocalcin in children with IDDM. Saggese et al found magnesium to play a pivotal role in this phenomenon. Supplementation of magnesium at 6mg/kg body weight in 23 IDDM children resulted in increased levels of calcium, magnesium, PTH, calcitriol, and osteocalcin.[101]

Tarui found diabetic patients exhibited elevated urinary zinc levels which were normalized with insulin treatment.[102] As mentioned previously, zinc may exert an insulin-like effect. Injections of zinc chloride to alloxan-induced diabetic rats prevented the hyperglycemia generally observed 24 hours after alloxan.[103] Zinc appears to protect islet cells from destruction as well as to enhance the effect of insulin when the two are given in tandem.

Kosenko found the mean manganese content of whole blood of diabetics to be one-half that of normal subjects.[104] Like zinc, manganese administration also prevented the post-alloxan rise in blood glucose. In the case of manganese, however, the beta cells were not protected from destruction. In this same study, neither chromium nor cobalt protected rats from the diabetogenic effects of alloxan.[103]

Other nutrient effects: Essential fatty acid metabolism is impaired in diabetics. Delta-6-desaturase, the enzyme necessary to convert linoleic acid to gamma-linolenic acid (GLA), is inhibited in diabetics. A one-year study of 111 diabetic patients with mild neuropathy was conducted by Keen et al. The group was divided, with half receiving 480 mg/day GLA and the other half receiving placebo. After one year the change for all 16 parameters measured was more favorable for the GLA group than the placebo group, with statistical significance for 13 of the parameters.[105]

GLA has been found to enhance nerve conduction and blood flow in diabetic rats. When GLA was bound to ascorbate to form ascorbyl gamma-linolenic acid the effect was

40 times greater than with evening primrose oil and significantly greater than with GLA and ascorbate given together.[106] The effectiveness of essential fatty acids appears to be related to the vasodilatory effects, which improve nerve conduction.[107] PGE1 is one of the end products of GLA metabolism. Intravenous. PGE1 has been found to improve both subjective symptoms and vibratory threshold in patients with diabetic neuropathy.[108] Diets high in linoleic acid appear to decrease the progression of microangiopathy in diabetics.[109]

It is advised that blood lipid levels be monitored when supplementing diabetics with essential fatty acids. In at least one study, supplementation of type-I diabetics with omega-3 fatty acids in the form of Max EPA resulted in an increase in total cholesterol. On the other hand, a study of 18 type-I diabetics supplemented with cod liver oil, rich in omega 3 fatty acids, resulted in an increase in HDL levels and a decrease in triglycerides and VLDL. There was no change in LDL level. Olive oil decreased LDL, but increased VLDL and triglyceride levels. In this same study, cod liver oil lowered blood pressure and partially normalized microvascular albumin leakage.[111] Beitz et al found cod liver oil at a dose of 6.8 g daily for two weeks decreased thromboxane B2 synthesis capacity of whole blood in type-I diabetics, but not in normal volunteers.[112]

Acetyl-L-carnitine (ALC) has been found to enhance peripheral nerve function by normalizing nerve conduction velocity in STZ-diabetic rats. One mechanism appears to be restoration of myo-inositol levels. Sorbitol levels in nerve cells remained high, however, so ALC was not acting as an aldose reductase inhibitor.[113] ALC also reduced elevated malondialdehyde content of nerve cells, which is an indication of reduced lipid peroxidation. These same researchers, in a different study, found ALC lowered sorbitol levels slightly, although they still remained high, and had no effect on myo-inositol levels.[114]

Lowitt et al found additional evidence that ALC works via another mechanism besides influencing the sorbitol pathway. An electroretinogram measures the changes in electric potentials in the retina in response to light. Rats with STZ-induced diabetes exhibited abnormal electroretinograms. ALC significantly improved ß-wave amplitudes and decreased latencies of oscillatory potentials without affecting hyperglycemia or erythrocyte sorbitol levels.[115]

The effect of lipotropic factors on diabetics was examined by Morrison. A combination of 9 g betaine, 660 mg choline, 660 mg liver extract, and 36 mcg vitamin B12 daily was found to have an insulin sparing effect on diabetics, reducing their insulin requirement.[116]

Franconi et al found that plasma and platelet taurine levels were low in IDDM patients. Oral supplementation raised levels to normal. They also found that the amount of arachidonic acid needed to induce platelet aggregation was lower in these patients than in healthy subjects. Supplementation of taurine reversed this effect as well, reducing the effect of arachidonic acid on platelet aggregation. *In vitro* experiments demonstrated that taurine reduced platelet aggregation in diabetic patients in a dose-dependent manner, and had no effect on healthy subjects.[117]

Pyridoxine alpha-ketoglutarate (PAK) has been found to lower blood glucose levels in diabetics. Passariello et al noted an average blood glucose decrease from 216 mg/dl to 169 mg/dl after two weeks, and to 153 mg/dl after four weeks. HbA1c levels also fell from an average of 13.9 to 11.3 after two weeks, and 9.4 after four weeks. There was no change in the placebo group. When PAK was discontinued, blood glucose and HbA1c returned almost to pre-treatment levels. Furthermore, PAK reduced blood levels of lactate 36.6% in type-I diabetics. Pyruvate levels were also decreased.[118] Although PAK's

Table 3. Botanical Applications In Diabetes

Botanical	Function
Gymnema sylvestre	Reduces insulin requirement and average blood glucose; reduces HbA1c; regeneration of pancreatic beta-cells (animals); lowers certain glycoproteins -- GAGs.
Vaccinium myrtillus	Lowers blood glucose; lowers triglycerides; decreases capillary permeability to prevent retinopathy; decreases abnormal glycoproteins.
Trigonella foenum graecum	Decreases urine glucose; lowers blood lipids;
Momordica charantia	Contains a polypeptide (p-insulin) with insulin-like effects; lowers blood glucose by increasing glucose utilization.
Coccinia indica	Lowers blood glucose by enhancing its utilization.
Tricosanthes dioica	Lowers blood glucose (animal models)
Ginkgo biloba	Membrane stabilization to prevent retinopathy
Agaricus bisporus	Improves hyperglycemic effects of exogenous insulin.

mechanism of action is not fully understood, it is believed that it may activate the Kreb's cycle, enhancing glucose metabolism and pyruvate oxidation. Whatever the mechanism, PAK appears to improve glucose metabolism and to decrease hyperlacticacidemia, thus preventing lactic acidosis. Researchers have observed in type-I diabetics physical exercise induces an immediate and sustained rise of lactic acid in the blood stream.[118] Dall'Aglio et al found infusions of PAK to type-I diabetics immediately prior to isometric exercise decreased the rise in serum lactate levels generally seen in response to exercise.[119]

Elevated homocysteine levels appear to be a risk factor for diabetic retinopathy.[120] This may be due to a point mutation on the gene for the enzyme methylenetetrahydrofolate reductase. This enzyme is important for remethylation and subsequent decrease of homocysteine levels. A significantly higher percentage of diabetics with retinopathy exhibit this mutation. Elevated homocysteine levels cause cell injury to small vessels which may contribute to the development of retinopathy, as well as causing macroangiopathy in the cardiovascular system.[120] On the other hand, Agardh et al found no association between plasma homocysteine levels and various stages of retinopathy or early stage nephropathy in IDDM patients.[121] Robillon et al observed, in comparing 41 type-I diabetics with 40 age-matched controls, that diabetics actually had lower homocysteine levels than controls, and that homocysteine levels increased with age.[122]

Hultberg et al found patients with proliferative retinopathy had higher than normal levels of homocysteine. In this group, those with minimal or no signs of nephropathy, while not as high as those with significant nephropathy (17.0 +/- 5.9 mumols/l), still exhibited slightly higher (12.1 +/- 5.5mumols/l) than normal (11.0 +/- 3.4 mumols/l) homocysteine levels.[123]

Elevated homocysteine levels, in patients with advanced nephropathy, are probably caused in part by decreased glomerular filtration rather than being a cause of the nephropathy.[123] Turyn et al found that insulin binding to rat submaxillary gland microsomes was enhanced in the presence of S-adenosyl-L-methionine (SAM) and was partially suppressed in the presence of S-adenosyl-L-homocysteine.[124] The release of

insulin in response to glucose was decreased in response to inhibitors of methylation such as DL-homocysteine, in rat pancreatic islet cells.[125] It is clear homocysteine contributes to diabetic complications in a subgroup of IDDM patients. The connection between elevated levels and development of secondary complications of diabetes bears further study.

Coenzyme Q is important in the electron transport chain of the mitochondria. Studies have found decreased levels of this group of enzymes in the liver mitochondria in diabetic animal models.[126] An oral dose of 10 mg Coenzyme Q7 for 3-13 weeks resulted in subjective relief of pain and paresthesia, as well as improvement in threshold of vibratory perception, in patients with diabetic neuropathy.[127]

Pantethine, a constituent of Coenzyme A and an active form of pantothenic acid, at a dose of 900 mg daily, has been shown to significantly lower total cholesterol, VLDL, and triglycerides in diabetic patients on dialysis.[128] Arsenio et al reported on a group of hyperlipidemic patients, a subfraction of whom were diabetics. Pantethine was administered at a dose of 300 mg three times daily, with consistent gradual reductions over 12 months of triglycerides, total cholesterol, LDL, and apolipoprotein B, and increases in HDL and apolipoprotein A, including in the diabetic subgroup.[129] These are all consistent with a decrease in atherogenesis. Shigeta et al studied the effect of 30-200 mg pantethine on vibratory perception thresholds in 16 patients with diabetic neuropathy.[130] Pantethine improved extremity paresthesias and pain in 33% of cases, and patellar reflex in 40%.[130]

For a concise summary of the nutrients discussed above, please see Table 2.

The Influence of Botanicals on Type-I Diabetes

The use of botanicals has a long history in folk medicine for the treatment of blood sugar abnormalities. Prior to the development of exogenous insulin in 1922, diabetes was managed with herbal medicines. Many plants have been investigated in the last two decades in response to the World Health Organization's 1980 request that researchers re-examine traditional medicines (see Table 3).

Gymnema sylvestre, a plant native to India, has been used for the treatment of diabetes or "madhu-meha" (honey urine) for over 2000 years, and has been relatively widely studied since the 1930s. A water-soluble extract of Gymnema leaf was administered to 27 type-I diabetics at a dose of 400 mg/day over a period of 10-12 months. Insulin requirements were decreased by about one half, and average blood glucose was reduced from 232 to 152 mg/dl. There was a reduction in HbA1c levels in the first 6-8 months, although the levels remained significantly higher than normal. Similar reductions were noted in other glycosylated proteins. Cholesterol and triglycerides were also lowered significantly, as was serum amylase, which is often more than doubled in diabetics. In patients on insulin therapy alone, fasting glucose, HbA1c, blood lipids, glycosylated proteins, and serum amylase remained high despite insulin therapy.[131] Numerous animal studies have corroborated these findings.[132-137]

A Gymnema extract doubled the number of islet and beta cells in the pancreas of STZ-treated rats, lending credence to the theory that it increases insulin secretion by regeneration of the endocrine pancreas.[136] Some animal studies found Gymnema to be effective in lowering blood glucose only in mild to moderately diabetic animals, those who still retained some beta-cell activity; however, treatment with Gymnema in a severely diabetic group significantly prolonged life.[137]

Abnormal glycoprotein composition of connective tissue basement membrane glycosaminoglycan (GAG) content has been implicated in diabetic complications such as microangiopathy and atherosclerosis.

Gymnema, in animal studies, lowered several glycoproteins, generally elevated in diabetics, to normal levels. GAGs which are typically high in diabetics (hyaluronic acid and heparin sulfate) were lowered after administration of Gymnema, while the GAGs which are generally depressed in diabetics (chondroitin sulfate-A,-B,-C) were elevated to normal.[134]

Vaccinium myrtillus (bilberry) has long been used for the treatment of diabetes. The biologically active constituents of bilberry include a family of flavonoids known as anthocyanosides. Bilberry has been shown to lower plasma glucose by 26% in STZ-diabetic rats.[138] In this same study, it also lowered triglyceride levels by 39%. While the hypoglycemic effects of bilberry are of interest in the treatment of diabetes, perhaps of more importance are its effects on stabilizing collagen[139] and decreasing capillary permeability.[140] Increased capillary permeability, resulting in retinal hemorrhage with resultant abnormal collagen repair, is an underlying cause of diabetic retinopathy. Bilberry can decrease abnormal collagen formation and capillary permeability, thus helping prevent retinopathy.[139]

Thirty-one patients with various types of retinopathy were treated with Vaccinium *myrtillus* extract. Reduction of both capillary permeability and tendency toward hemorrhage were seen in all patients, particularly those with diabetic retinopathy.[141] Fifty-four diabetic patients were treated with 500-600 mg/day of the extract for 8-33 months. Almost total normalization of collagen polymers was achieved, as well as a 30% decrease in structural glycoprotein.[142] Via similar mechanisms, oligomeric proanthocyanidins from the seeds of *Vitis vinifera* may help prevent diabetic retinopathy.[143]

Trigonella foenum graecum (fenugreek) has been studied, particularly in India, for the treatment of diabetes. Defatted fenugreek seed powder was given to IDDM patients at a dose of 100 grams daily in two divided doses over a 10-day period. The fenugreek-treated group exhibited a 54% decrease in 24-hour urinary excretion of glucose, as well as a reduction in total cholesterol, LDL, VLDL, and triglycerides.[144] Animal studies have also demonstrated the hypoglycemic and hypolipidemic effects of fenugreek.[145-149]

Momordica charantia (bitter melon, bitter gourd) is commonly found in China, India, and Africa, where it has a history of medicinal use.[150] The active, hypoglycemic constituents include charantin, obtained from an alcohol extract of the fruit, and a polypeptide called p-insulin (plant insulin or polypeptide-p) isolated from the fruit and seeds of the plant. The p-insulin consists of 166 residues containing 17 amino acids and has a molecular weight of 11,000.[151] It is structurally and pharmacologically comparable to bovine insulin, and is composed of two polypeptide chains with disulfide bonds. [150] Baldwa, et al studied the effect of p-insulin on nine diabetic patients and found an onset of action similar to bovine insulin (30-60 min.) and a peak hypoglycemic effect after 4 hours in type I diabetics, compared with 2-3 hours for regular insulin.[151] Several animal studies have confirmed the blood-sugar lowering effects of Momordica extracts[152-155] while others have not.[155] The hypoglycemic effects of this plant appear to be, at least in part, due to extra-pancreatic activity, including increased glucose utilization by the liver;[153] decreased glucose synthesis by depression of key gluconeogenic enzymes glucose-6-phosphatase and fructose-1,6-biphosphatase; and enhancement of glucose oxidation through the shunt pathway via activation of glucose-6-phosphate dehydrogenase.[154]

*Coccinia indica***,** in animal studies, has demonstrated blood-glucose lowering effects which appear to be via the same mechanism as *Momordica.*[154,155] *Tricosanthes dioica* has also demonstrated blood-sugar lowering effects in experimental animal models.[157] *Ginkgo biloba* contains membrane stabilizing flavones and anthocyanosides which, in animal studies, have been shown to prevent retinopathy.[158]

An animal study of the effects of twelve plants used traditionally in Europe for the treatment of diabetes yielded the following results: *Arctium lappa* (burdock) and *Urtica dioica* (stinging nettle) aggravated the diabetic condition; *Anacardium occidentale* (cashew), *Taraxacum officinale* (dandelion), *Sambucus nigra* (elder), *Trigonella foenum-graecum* (fenugreek), *Humulus lupulus* (hops), *Catharanthus roseus* (periwinkle), *Salvia officinale* (sage), and *Daucus carrota* (carrot) had no effect on glucose homeostasis; and *Ilex guayusa* (guayusa) and *Agaricus bisporus* (cultivated mushroom) retarded the development of hyperglycemia in STZ-diabetic mice, and reduced glycosylated hemoglobin, polydipsia, and weight loss. Mushroom also improved the hypoglycemic effects of exogenous insulin.[159] Other researchers also found *Urtica dioica* to exert a hyperglycemic effect in animal models.[160]

Many other plants have been found to exert hypoglycemic effects but only in type-II diabetics (which will be the subject of a future article). In animal models, differentiation is made by inducing either mild diabetes, which is meant to parallel type-II diabetes, or severe diabetes, the equivalent of type-I diabetes, in which there is little or no beta-cell activity remaining. See Table 3 for a summary of botanicals in the treatment of IDDM.

Dietary Factors in the Treatment of IDDM

Much of the research on dietary management of diabetes has centered on type-II diabetics, primarily because this type may be prevented and controlled by dietary changes alone. The ingestion of a high complex carbohydrate, moderate protein, low fat diet versus a diet higher in fat and protein and very low in carbohydrate is controversial and undoubtedly depends on the individual and the type of diabetes in question. The research on the pros and cons of each type of diet will be the subject of a future article on type-II diabetes. Originally the ADA promoted a low carbohydrate, high protein, moderate fat diet for patients with diabetes. After considerable research was published on the benefits of a high complex carbohydrate, high fiber diet on the glycemic index and lipid profiles in diabetes, the ADA began advocating diets containing 55-60% calories from carbohydrates.[161]

A high fiber, high complex carbohydrate, low fat diet with the addition of 4.2 grams of gel fiber, in the form of glucomannan, was found to significantly improve glycemic control, insulin requirement, and HDL cholesterol levels in IDDM patients but not in patients on oral medication.[162] In another study, seven grams apple pectin in a shake with skim milk and vanilla given 10 minutes before a meal, decreased by 35% the insulin required to return glucose levels to normal in IDDM.[163]

Sixteen grams guar gum and 10 g pectin was added to a meal containing 106 g carbohydrate. This meal significantly decreased the postprandial glucose rise in three type-I diabetics.[164] Other researchers have not found pectin to help with long-term blood sugar control as measured by HbA1c.[165] In type-I diabetics, it appears it is not the high complex carbohydrate diet that is a factor in glycemic control so much as the type and amount of fiber being consumed. On the basis of food diaries, diabetic patients without retinopathy ate significantly more complex carbohydrates, water-soluble fiber, insoluble fiber, and glucose, and a lower proportion of calories from protein than did patients with retinopathy.[166] Both water soluble and insoluble fiber significantly lowered mean postprandial glucose levels in diabetic dogs.[167]

As mentioned above in the discussion of cow's milk, diet may be a contributing factor in the development of type-I diabetes. A Swedish study examined the diets of 339 children age 1-14 with newly-diagnosed

IDDM, and compared them with 528 age- and sex-matched controls. Foods were classified according to the protein, fat, carbohydrate, monosaccharide or disaccharide, nitrosamine, nitrate or nitrite, vitamin C, and fiber content, with the frequency of intake categorized as high, medium or low. The relative risk of developing IDDM was calculated for the three frequencies of intake. The results indicated that diets high in protein, carbohydrate (not differentiated by type) and nitrosamine compounds may influence the risk of developing IDDM in childhood.[168]

General Lifestyle Factors

Smoking influences carbohydrate and lipid metabolism. In a group of insulin-treated diabetics, 114 smokers were compared to 49 non-smokers. Smokers had a 15-20% higher insulin requirement and serum triglyceride concentration. This increase rose to 30% in heavy smokers.[169]

Exercise may result either in hyper- or hypoglycemia. In type-I diabetics, exercise prompts an immediate release of lactic acid (as noted above) as well as glucagon.[119] This release of glucagon may explain the rise in blood sugar noted by many type-I diabetics upon physical exertion. A rise in blood sugar upon exercise occurs particularly in those individuals with blood sugar levels above 250 mg/dl at the onset of exercise.[170] This can result in ketoacidosis. Urine ketone levels should be checked before intense exercise is undertaken by these patients. Another risk of exercise in diabetics, particularly those over age 40, is the possibility of unmasking an existing cardiovascular problem. Ocular complications may also be precipitated by vigorous exercise in diabetics.

Exercise may benefit IDDM patients as well, by helping to lower blood glucose levels, increasing insulin sensitivity,[170] and improving cardiovascular functioning. In diabetics who maintain tight glucose control, exercise will have the effect of lowering blood sugar. Care must be taken, however, as exercise may precipitate a hypoglycemic episode. Assuming blood sugar levels are normal prior to taking insulin, the preprandial dose may need to be cut 30-50% when moderate exercise is anticipated.[170]

Conclusion

Prevention of type-I diabetes is an exciting area of investigation, enabled by screening methods more sophisticated than were available in the past. Three large clinical trials are planned or underway to determine whether early intervention can prevent IDDM in persons at risk but who have not yet demonstrated clinical signs of disease: The Cow's Milk Avoidance Trial, the Diabetes Prevention Trial - Type-I (testing the use of insulin on persons who have not yet manifested the disease), and the European Nicotinamide Diabetes Intervention Trial. Depending on the results of these trials, large-scale screening of children for IDDM risk factors may be warranted.

There is considerable evidence that supplementation of type-I diabetics with specific nutrients and botanicals may significantly impact their chances of developing complications including micro- and macroangiopathy, retinopathy, nephropathy, neuropathy and cataracts. In addition, the use of botanicals and nutrients may significantly decrease insulin requirements. Among the most promising nutrients are the B vitamins, vitamins C and E, chromium, zinc, magnesium, vanadium, lipoic acid, pyridoxine alpha-ketoglutarate, acetyl-L-carnitine, pantethine, quercetin, and essential fatty acids. Botanicals which appear to be beneficial in the treatment of type-I diabetes include *Gymnema sylvestre, Vaccinium myrtillus, Trigonella foenum graecum,* and *Momordica charantia.* Dietary interventions should include complex carbohydrates in the form of water soluble fibers, such as pectin and guar gum. Blood sugar levels should be

checked before initiation of exercise and insulin doses adjusted accordingly.

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