AN INTEGRATIVE APPROACH TO THE MANAGEMENT OF TYPE 2 DIABETES MELLITUS

Ben Kligler, MD, Darren Lynch, MD

DESCRIPTION

Although the incidence of type 2 diabetes mellitus is rapidly rising in the US concurrent with the epidemic of obesity, there is strong evidence that it may be prevented in high-risk patients through aggressive lifestyle interventions. This lesson is designed to discuss the role of medications, diet, exercise, mind-body approaches, botanical medicines, and nutritional supplements in managing the disorder.

TARGET AUDIENCE

Healthcare providers who practice or who are interested in practicing nutritionally-oriented, integrative medicine.

OBJECTIVES

Upon completion of this article, participants will be able to do the following:
1. Identify the significance of insulin resistance and glycemic index scores
2. Discuss the principles of dietary revision for diabetic patients
3. List nutrients that are believed to be associated with improved glucose sensitivity

Diabetes mellitus is a disorder characterized by an inability to properly transport and metabolize glucose. This inability can have a number of causes depending on the type of diabetes, but the final common pathway of all types is an elevated plasma glucose. In type 1 diabetes (formerly known as “juvenile onset” or “insulin-dependent”), this inability is caused by a failure of insulin production in the pancreas; in type 2 diabetes, the problem is insulin resistance and decreased sensitivity of the insulin receptor. Both types of diabetes if uncontrolled can lead to end-organ damage to the eyes, the kidneys, the heart, the nerves, and the microvasculature. These end-organ consequences are responsible for much of the burden of disease in the diabetic population. For example, diabetes is currently the number one cause of blindness, end-stage kidney failure, and circulatory problems leading to amputation. Yet a third type of diabetes is gestational diabetes, which is diabetes occurring during pregnancy.

Because these 3 types of diabetes are very different in origin, and because a thorough discussion of the treatment of all is beyond the scope of this article, we will focus here primarily on the integrative medicine approach to prevention and treatment of type 2 diabetes. We will however briefly review the epidemiology and pathophysiology of type 1 diabetes and gestational diabetes as well as type II. The metabolic syndrome of insulin resistance (syndrome X) which often precedes a diagnosis of type 2 diabetes will also be discussed here.

Definition

The American Diabetes Association and the World Health Organization have used a fasting plasma glucose (FPG) concentration of 126 mg/dL (7.0 mmol/L) as the primary diagnostic criteria for the presence of diabetes. A random glucose measurement of over 200, if accompanied by symptoms, is also diagnostic, as is an abnormal response to a glucose tolerance test.

Pathophysiology and Prevalence

Type 1 diabetes mellitus, which accounts for less than 10% of all cases, is primarily a failure of insulin production resulting from an autoimmune destruction of the pancreatic islet cells responsible for insulin secretion. Antibodies against pancreatic cells are found in approximately 85–90% of individuals with type 1 diabetes mellitus. In this form of diabetes, the rate of islet cell destruction can be variable, being rapid in some individuals and slow in others. Autoimmune destruction of islet cells can be the result of a genetic predisposition, environmental factors and in some cases, unknown causes. Individuals with type 1 diabetes are at risk for the development of other autoimmune disorders such as Graves’ disease and pernicious anemia.

Type 2 diabetes, once referred to as non-insulin dependent or adult-onset, accounts for the vast majority of patients with diabetes; in the United States, approximately 16 million persons...
have type 2 diabetes mellitus. The incidence of type 2 diabetes mellitus is rising rapidly concurrent with the epidemic of obesity in this country, and has approximately tripled over the past three decades. More alarming is the recent steady demographic shift in type 2 diabetes to younger populations. According to a recent estimate from the Center for Disease Control (CDC) the incidence of diabetes has increased almost 40% for those under 50 and almost 70% for those under 40. Unlike in type 1 diabetes mellitus, these individuals do not have antibodies to their islet cells but become resistant to utilizing the insulin they produce. At least initially, these individuals do not need insulin treatment. Obesity plays a large role in the pathogenesis of type 2 diabetes, as it contributes to insulin resistance; a number of factors secreted by fat cells (leptin, tumor necrosis factor, and others) increase insulin resistance and thus interfere with the action of insulin.

Gestational Diabetes

Gestational diabetes mellitus (GDM) occurs in approximately 4% of all pregnancies in the US, and can lead to fetal macrosomia, shoulder dystocia and metabolic problems in the newborn. Clinical recognition of GDM is important because treatment and antepartum fetal surveillance can reduce perinatal morbidity and mortality. Risk assessment for GDM should be part of the first prenatal visit. Current practice is to screen all women for GDM between 24 and 28 weeks gestation; women at high risk because of strong family history, prior GDM, unexplained prior intraterine death, or abnormal fasting glucose prior to pregnancy should be screened earlier.

Insulin Resistance/The Metabolic Syndrome

There is now a great deal of evidence that the insulin resistance which characterizes type 2 diabetes mellitus—and which is almost certainly present in most patients for a number of years prior to diagnosis—can have a number of other significant effects in the body which can increase the long term risk of heart disease and cancer. These include elevation of LDL and depression of HDL, a tendency to hypertension, and obesity. This constellation is known as "Syndrome X" or the "Metabolic Syndrome," and is known to significantly increase the risk of cardiovascular disease and other end-organ dysfunction. The prevalence of Syndrome X in the general population is not known, but it is almost certainly significantly more common than overt type 2 diabetes mellitus.

Fortunately, the approaches to prevention described below, which are proving to be potentially very effective in delaying time to onset or preventing onset entirely of type 2 diabetes mellitus are also very effective in treating the metabolic syndrome and decreasing the tendency toward insulin resistance in these patients.

PREVENTION

There is now no doubt that type 2 diabetes mellitus can be prevented in many of those at high risk for the disorder through an aggressive lifestyle intervention approach. Risk factors for Type II DM are now well defined and include obesity (BMI over 25), lack of physical activity, poor diet (excessive calories, low fiber intake, high intake of saturated and trans fats, high glycemic load, high glycemic index), cigarette smoking, and abstinence from alcohol consumption. These risk factors often manifest as impaired glucose tolerance prior to the development of frank diabetes in those at high risk for the disease.

A number of intervention trials have now clearly demonstrated that the incidence of diabetes can be significantly reduced through aggressive lifestyle intervention in those at high risk for the disorder. In a landmark Finnish trial, an intervention consisting of individualized counseling aimed at weight reduction, reduction of total fat and saturated fat intake, increased intake of fiber, and increased physical activity was studied in a cohort of 522 subjects with impaired glucose tolerance. At four years of follow-up, the cumulative incidence of diabetes in the intervention group was 11%, versus 23% in the control group, representing a 50% reduction in the risk of diabetes over that time period. Average weight loss in the first two years in the intervention group—who started with a markedly increased mean BMI of 31—was only 3.5 kilograms, suggesting that even modest weight loss can have a very substantial impact on diabetes risk. Earlier non-randomized studies of similar interventions in high-risk populations in China and Sweden found similarly decreased incidence of new-onset diabetes.

Although physicians are often pessimistic about the likelihood of their patients being able to adhere to an aggressive program of lifestyle change, the integrative approach—with its emphasis on mobilizing the intrinsic healing potential and inner resources of each patient—requires that such an approach to prevention for those at high risk of diabetes form the cornerstone of therapy. In fact, the intervention for those in the treatment group in the Finnish study was relatively modest, consisting of 7 sessions with a nutritionist during the first year, and one session every 3 months thereafter, as well as individualized guidance on how to increase physical activity.

Table 1 outlines the specifics of the successful lifestyle intervention program tested in the Finnish trial. One additional new development in diabetes care—the concept of “group care”—may be particularly relevant to the implementation of a prevention-oriented intensive lifestyle intervention program. Researchers in Turin Italy have recently shown that the use of interactive group visits for following lifestyle intervention in patients with diabetes is more effective—and not significantly more expensive—than individual care.

TREATMENT

Conventional Treatment Options

For new onset diabetes in which symptoms are minimal, a trial of dietary modification, weight loss, and exercise as described above is indicated as the first step. Consultation with a nutritionist, and ideally with a professional qualified to advise on exercise regimens, should be part of this strategy. Initial assessment should include investigation for any evidence of end-organ damage to the eye, the heart, the kidney, the nerves or the microvasculature. Assessment for the presence of the other elements of the Metabolic Syndrome

Table 1 Elements of lifestyle intervention in the Finnish Diabetes Prevention Study

<table>
<thead>
<tr>
<th>Description</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight reduction</td>
<td>&gt;5%</td>
</tr>
<tr>
<td>Total fat intake</td>
<td>&lt;30% of total energy</td>
</tr>
<tr>
<td>Saturated fat intake</td>
<td>&lt;10% of total energy</td>
</tr>
<tr>
<td>Fiber intake</td>
<td>&gt;15g per 100kcal</td>
</tr>
<tr>
<td>Moderate exercise</td>
<td>for at least 30 minutes per day</td>
</tr>
<tr>
<td>Frequent ingestion</td>
<td>of whole grain products, vegetables, fruits, low-fat milk and meat products, soft margarines and vegetable oils rich in monounsaturated fats</td>
</tr>
</tbody>
</table>
Syndrome, such as hyperlipidemia, is also critical, and should be followed by institution of proper treatment for these abnormalities.15

Conventional pharmaceutical therapy falls into several categories, and will not be discussed here in depth. Oral hypoglycemic medications are generally used as first line therapy if lifestyle interventions are not sufficient.

There are 5 classes of diabetes drugs sold in the US: sulfonylureas, meglitinides, biguanides, thiazolidinediones, and alpha-glucosidase inhibitors. Sulfonylureas and meglitinides stimulate the beta cells of the pancreas to release more insulin. Biguanides lower blood glucose levels by decreasing the amount of glucose produced by the liver and by lowering blood glucose levels by making muscle tissue more sensitive to insulin so glucose can be absorbed. Thiazolidinediones help insulin work better in the muscle and fat and also reduce glucose production in the liver. Alpha-glucosidase inhibitors lower blood glucose levels by blocking the breakdown of starches in the intestine.16

Because sulfonylureas and meglitinides stimulate the release of insulin, they may cause hypoglycemia (low blood glucose levels). Chlorpropamide, and other sulfonylureas, can interact with alcohol to cause vomiting, flushing, or sickness. Metformin, a biguanide, may cause diarrhea. Thiazolidinediones can have a rare but serious effect on the liver; regular blood tests are required of those taking the drug. Alpha-glucosidase inhibitor may have side effects as well, including gas and diarrhea.16

If oral medications fail then patients will be started on insulin, often in combination with an oral agent. The generally agreed upon target for glycemic control in type 2 diabetics is a glycohemoglobin under 7.0%.

The important role of angiotensin-converting-enzyme inhibitors (ACEI) in preventing progression of renal disease in patients with diabetes is now well documented.17 Many physicians now feel that any patient who cannot lower his or her HGBA1C entirely into the normal range should probably be offered an ACEI as part of the treatment of diabetes; however because a low glycemic index (LGI) diet is so clearly beneficial in lipid control and in a number of the other metabolic abnormalities which often accompany diabetes, it is described below as a useful option in diabetes particularly for those patients presenting with the other metabolic abnormalities of Syndrome X accompanying their glucose intolerance. Interestingly, the Women’s Health Study has demonstrated that contrary to popular belief, sugar intake per se (defines as sucrose, glucose, fructose and lactose) does not increase risk of diabetes.18

Fiber

Low fiber intake has been shown in multiple studies—including the Nurses Health Study and the Health Professionals Study—to be a risk factor for development of diabetes.19-21 When combined with a high glycemic load (an indicator of global insulin demand based on dietary intake, calculated by multiplying the GI value of a food by the amount of carbohydrate per serving and dividing by 100) the relative risk of a low fiber diet is on the order of 2.5.20 Other population-based studies have also reported inverse associations between dietary fiber and serum insulin,22 and fiber has been shown in intervention studies to decrease both postprandial glucose and insulin concentrations in patients with or without diabetes.23 Although total fiber intake is important, low intake of cereal fiber appears to be most strongly associated with diabetes risk. Interestingly, the one study which examined the protective role of cereal fiber specifically in African Americans compared to whites (n=12,251) found that although the benefit found in other studies was apparent in whites (RR=0.75) it did not appear in the African American population studied.24 Given the high prevalence of diabetes in African Americans, this question will need further study.

A small intervention trial examined the impact of increasing fiber on glycemic control in a group of type 2 diabetics (n=13, crossover design), comparing a diet with moderate amounts of fiber (8g soluble/16g insoluble, as recommended by the American Diabetes Association) with a high fiber diet (25g soluble/25g insoluble). The high fiber diet led to a reduction in fasting glucose of 13mg/dl, as well as reducing cholesterol (6.7%), triglycerides (10.2%) and very-low-density lipoproteins (12.5%).25

For patients who need fiber above and beyond what they are able to incorporate in to their diet, two plant-based fiber supplements—psyllium and glucomannan—are discussed below in the section on botanical medicines.

Whole grains

Whole vs. refined grains have been clearly demonstrated to decrease the risk of diabetes in a number of large cohort studies.26-28 The relative risk when the highest level of whole grain consumption is compared to the lowest in these studies is on the order of 0.6. It is not totally clear if this effect is completely independent of the effect of fiber and serum magnesium—both of which are present in whole (but not refined) grains, and both of which also decrease risk of diabetes—although some investigators do find the benefit of whole grains to persist even when adjusting for these components.29 In the Framingham Offspring Study (n=2941), high intake of whole grains was inversely associated with a number of metabolic risk factors, including BMI, fasting insulin levels, LDL cholesterol and waist-hip ratio, suggesting that increasing whole grain intake may be a way to address several dimensions of the Metabolic Syndrome simultaneously.30 There are no published prospective intervention trials of increasing whole grain consumption per se as a strategy for controlling diabetes.

Dietary fats

The proper balance of saturated to polyunsaturated to mono-unsaturated fats in the diet plays a central role in the dietary recommendations both for prevention and treatment of diabetes. A total intake of fats at less than 30% of calories, and a restriction in saturated fats to less than 10% of total calories have been shown to be effective dietary interventions in the prevention trials to date. The benefit of the restriction in overall fat calories in diabetes pre-
vention is most likely related to the effect of fats on total calories and on weight control.

Recent data from the Nurses’ Health Study suggests that more emphasis on nuts as a source of monounsaturated and polyunsaturated fats may reduce risk of diabetes in women. Women in the highest category of nut and peanut butter consumption in this cohort study had a significantly reduced risk of developing diabetes (RR=0.73 for nuts, 0.79 for peanut butter) over the 16 year follow-up period of this study. The role of omega three essential fatty acids and specifically fish oils in diabetes is discussed below in the section on nutritional supplements.

Low Glycemic Index Diet

The glycemic index (GI) is a ranking of foods on a scale from 0 to 100 according to the extent to which they raise blood glucose and insulin levels after eating. Carbohydrate foods that break down quickly during digestion have the highest glycemic indexes, generating a rapid rise in blood glucose. Carbohydrates that break down slowly release glucose gradually into the blood stream, and have low glycemic indexes. To determine a food’s GI rating, measured portions of the food containing 50 grams of carbohydrate are fed to people after an overnight fast. Finger-stick blood glucose samples are taken at 15-30 minute intervals over the next 2 hours. The GI rating of the test food is calculated by dividing the blood glucose response for the test food by that of a reference food (generally white bread or glucose) and multiplying by 100. The average of the GI ratings from all subjects is published as the GI of that food.

A low GI diet is characterized by the exclusion of foods ranked high in glycemic index, and the inclusion of foods ranked low or moderate in glycemic index. This diet can increase insulin sensitivity in some subjects, help with weight loss, lower blood lipids, and may even be of benefit in cancer risk reduction by decreasing insulin-like growth factor. The reduction of risk of coronary heart disease in relationship to the overall glycemic index of the diet is now fairly clear; the relationship between diabetes risk and GI is somewhat less clear. Some of the large cohort studies do find elevated GI to be a risk factor for diabetes, others do not find such a relationship, and the risk if it exists is not nearly as clear as that described above for a diet low in fiber and whole grains.

Two recent intervention trials on LGI diets add somewhat to this confusion. In one, a very simple and practical intervention—a low GI breakfast—was tested in a group of diabetic men (n=13, crossover design) and found to modestly lower blood glucose and improve lipid profiles over a 4 week period. A second trial (n=45) randomized subjects with diabetes to either a high GI diet or a low GI diet for eight weeks. All diets were low in calories (1440 kcal/day) and saturated fat (<5% of calories). Weight loss was equivalent between the two groups, as was the improvement in glycemic control. LDL was reduced significantly more in the LGI group.

The most important effect of the LGI diet in diabetes may be mediated by its impact on weight control through its effect on overeating. Diets of differing GI (low vs. high) were investigated to evaluate the effect of GI on overeating in non-diabetic obese adolescent males. Voluntary energy intake after the high-GI meal was 53% greater than after the medium-GI meal, and 81% greater than after the low-GI meal. In addition, compared with the low-GI meal, the high-GI meal resulted in higher serum insulin levels, lower plasma glucagon levels, lower post absorptive plasma glucose and serum fatty acids levels, and elevation in plasma epinephrine. Therefore, the high GI diet, by causing persistently elevated insulin levels, may lead to more unconscious overeating in a viscous cycle of weight gain ultimately increasing the risk of diabetes.

Summary of Dietary Recommendations

The controversy over whether total calories, fat calories, or glycemic index are most important in control of diabetes notwithstanding, the basics of a healthy diet for patients with this condition are now fairly clear. The fat profile of the diet should be high in monounsaturated fats, with moderate polyunsaturated and low saturated fatty acid and trans fatty acid content. The diet should be high in fiber (goal of 50g per day) and provide adequate protein. A macronutrient content of the diet of approximately 40% carbohydrates, 30% protein and 30% fat is commonly used, and calories can be adjusted accordingly as indicated. Refined grains are eliminated and whole grains are emphasized. Starchy vegetables are restricted but non-starchy vegetables are unrestricted. Fruits with high glycemic index are limited and low and moderate glycemic index fruits are encouraged in moderate amounts to minimize glycemic load. Legumes are emphasized due to their low glycemic index. Lean proteins, fatty fish, and nuts are encouraged. Weight control is a high priority, as even weight loss on the order of 5% of body weight can make an enormous difference in glycemic control.

Exercise

Lack of exercise is clearly established as a risk factor for development of diabetes in susceptible individuals. The Finnish, Chinese, and Swedish intervention/prevention trials all included exercise as a critical component. In the Finnish trial, achieving the target of 4 hours of moderate physical activity per week was associated with a significant decrease in risk of diabetes even in those patients who were not successful in losing weight. Similarly a meta-analysis of 14 studies evaluating the impact of exercise on established diabetes found that exercise reduced HgbA1C from 8.3% to 7.6%—a significant decrease—even though it did not lead to a significant change in BMI.

Most experts agree that the exercise regimen recommended for those with diabetes should be aimed at both increasing cardiorespiratory fitness and muscle strength. Walking, jogging, swimming, aerobics, and circuit-type resistance training have all been successful strategies, and 4 hours total per week is generally agreed upon as a reasonable target. Many investigators feel that other types of moderate physical activity—household work, work-related physical activity, gardening—are probably as effective as structured exercise and can reasonably be included in the four-hour per week recommendation. Finally, Nurses’ Health Study investigators have also found that television watching is a major risk factor for obesity and diabetes in adults, independent of exercise levels: each 2-hour/day increment in TV watching was associated with a 23% increase in obesity and a 14% increase in risk of diabetes. Inquiring and counseling specifically regarding hours of television watched per day may be an important part of the integrative approach to preventing diabetes.

NUTRITIONAL SUPPLEMENTS

Vitamin E

Persistent hyperglycemia in diabetics is thought to trigger increased free radical mediated oxidative stress. Vitamin E is a potent

Integrative Approach to the Management of Type 2 Diabetes Mellitus
Magnesium
Magnesium functions as an essential cofactor involved in glucose oxidation and modulates glucose transport across cell membranes. In a large cohort observational study of 12,128 non-diabetic middle aged adults, low serum magnesium has been demonstrated to be an independent predictor of incident type 2 diabetes. Diets low in magnesium are associated with increased insulin levels and clinical magnesium deficiency is associated with insulin resistance. A recent randomized double-blind placebo-controlled trial of 63 type 2 diabetics with decreased serum magnesium treated with the sulfonylurea medication glibenclamide found that those treated with a magnesium chloride solution showed significantly higher serum magnesium concentration and lower fasting glucose levels and HbA1C than the control group. Overall, studies investigating the ability of magnesium to impact glycemic control have been mixed.

Magneism deficiency has been associated with increased incidences of hypertension, cardiovascular disease, and dyslipidemia as well. An inverse relationship has been found between magnesium levels and hypertension in both diabetics and non-diabetics. Because magnesium is predominantly an intracellular ion, assessment of deficiency by serum levels is not a very specific indicator. Red blood cell magnesium, perhaps a more valid measurement, was employed in a few of the investigations. Caution should be employed in supplementing patients with impaired renal function, as hypermagnesemia is a potentially fatal syndrome, characterized by hypotension, cardiac arrhythmias, CNS depression and possibly death. At this point no firm recommendations for magnesium supplementation in diabetes can be made, though advice may be to limit use in renal compromise and to use more bioavailable forms such as magnesium citrate, chloride, or glycinate in a dose of 400 mg daily maximum to avoid the major side effect of diarrhea.

Chromium
Chromium is an essential element required for normal carbohydrate and lipid metabolism. Signs of chromium deficiency include elevations in glucose, insulin, cholesterol, and triglycerides, and decreased HDL, all of which can improve with supplementation. Its mechanism of action has been described as increasing insulin binding to cells due to increasing the number of insulin receptors. In vitro studies have also shown chromium to alter activity of phosphotyrosine phosphatase and phosphotyrosine kinase.

The largest double-blind, placebo-controlled trial of chromium involved 180 Chinese type 2 diabetics, randomized to placebo, 200 mcg, or 1,000 mcg of chromium picolinate daily for 4 months. HgA1C levels significantly declined in both study groups at 4 months compared to placebo (placebo 8.5%, 200mcg 7.5%, 1,000 mcg 6.6%), yet the higher dose group also demonstrated significant improvements in fasting blood glucose levels, 2 hr oral glucose tolerance testing, and insulin and cholesterol levels. A follow up open-label study on 833 Chinese diabetics using a similar form of chromium, followed for 10 months, found decreases in fasting and post-prandial glucose as well as decreased symptoms of fatigue, excessive thirst, and frequent urination. Positive results have also been demonstrated with organic chromium in brewer’s yeast and chromium chloride. A recent meta-analysis based on data from 15 studies and 618 total participants, concluded that there was no effect of chromium on glucose or insulin concentrations in nondiabetic subjects and that the data for persons with diabetes is inconclusive. All of these studies have demonstrated safety and tolerability of chromium, though in a single study chromium picolinate was found to alter the levels of neurotransmitters, which may have an impact on patients with co-existing mental illness. Chromium appears to be a safe, potentially useful supplement in diabetics, though the optimal form and dose have yet to be determined.

Vanadium
Vanadium is a non-essential trace nutrient and a human deficiency syndrome has not yet been documented. In animal models, vanadium has been demonstrated to facilitate glucose uptake and metabolism, facilitate lipid and amino acid metabolism, improve thyroid function, and enhance insulin sensitivity. Human models have shown insulin-mimetic actions, enhancing insulin activity and increasing insulin sensitivity by upregulation of insulin receptors.

Two small studies of short duration in type 2 diabetics have demonstrated beneficial effects, principally reduction in fasting plasma glucose and HgA1C and increased insulin sensitivity without changes in insulin levels. A recent noncontrolled open-label study of 11 type 2 diabetics treated with vanadyl sulfate at higher dose (150 mg/day) and for a longer period of time (6 weeks) than previous studies found improved glycemic control through increased hepatic and muscle insulin sensitivity. Patients in all of the trials commonly reported nausea, vomiting, flatulence, cramping and diarrhea. Animal studies using high doses of vanadion have reported toxic liver and kidney effects. Organic vanadium compounds may be safer than their inorganic counterparts, with less documented GI intolerance and no reported renal or hepatic toxicity. Given the potential for toxicity, at least from the animal studies, and lack of available randomized controlled trials, recommendation for vanadium supplementation at this point may be premature. More studies of longer duration and a better understanding of its safety profile are necessary.

L-carnitine
Several in vitro studies have suggested that L-carnitine acts as a modulator of fuel substrate oxidation in cells, influencing free fatty acid and glucose oxidation. It has been the subject of much
research in the last few years, primarily in Italy, investigating its potential ability to help prevent diabetes. A study of 18 type 2 diabetic patients treated with intravenous acetyl-L-carnitine and placebo on alternate days demonstrated enhanced glucose uptake and storage. Another study suggests that carnitine may help prevent diabetes-induced cardiac autonomic neuropathy. The largest study investigating carnitine in diabetes was a multicenter randomized double-blind placebo-controlled trial involving 333 subjects meeting clinical and/or neurophysiologic criteria for diabetic neuropathy. Acetyl-L-carnitine (or placebo) was initially given IM for the first 10 days in a dose of 1000 mg, followed by 1 year of an oral daily 2000 mg dose. Nerve conduction was measured at 6 and 12 months, and pain was recorded by a visual analogue scale. Significant improvements were found in both parameters, leading the authors to conclude that acetyl-L-carnitine may be a viable treatment option for diabetic neuropathy. No side effects were noted in any of the above-mentioned studies. Though these preliminary studies are promising, further studies are necessary to support these findings as well as determine optimal dosing for L-carnitine.

**Alpha-lipoic acid**

Alpha-lipoic acid is a potent lipophilic antioxidant, unique in that it functions in both water and fat. This feature provides alpha-lipoic acid with an exceptionally broad spectrum of antioxidant action. It functions naturally as a co-enzyme in carbohydrate metabolism within the mitochondrial enzyme complexes. Alpha-lipoic acid has been used for decades in Germany to treat diabetic peripheral neuropathy. Studies involving alpha-lipoic acid have focused on glycemic control as well as diabetic neuropathy. A preliminary open trial of 20 diabetic patients using a twice-daily 600 mg oral dose showed an improvement in glucose metabolism. A systematic review of 15 studies of alpha-lipoic acid, all using different forms of the supplement and for different durations, found overall positive effects and excellent tolerability.

The recently published SYDNEY trial, a large randomized double-blind, placebo-controlled study investigating alpha-lipoic acid in diabetic neuropathy, involved 120 patients with symmetric sensorimotor polyneuropathy. These subjects were treated with 5 intravenous infusions per week for 14 total treatments. The study’s primary end point was sum score of daily assessments of severity and duration of neuropathy symptoms, with findings of statistical improvement in neuropathy symptom scores compared to placebo. The investigators concluded that IV alpha-lipoic acid, rapidly and to a significantly meaningful degree, improved the signs and symptoms of diabetic neuropathy compared to placebo. Though further studies are needed, alpha-lipoic acid may become an important supplement for diabetic patients.

**Soy**

Phytoestrogen consumption has been demonstrated to reduce risk factors for cardiovascular disease and soy protein consumption has become a part of many heart-healthy dietary recommendations. A crossover trial of a soy-based dietary supplement was undertaken in 20 type 2 diabetics, seeking to discover effects on lipid levels and cardiovascular risk markers. Subjects were randomized to supplementation of a soy protein supplement (50 g/day) or placebo for 6 weeks separated by a 3 week washout period. Statistically significant improvements were found in LDL, apolipoprotein B100, triglycerides, and homocysteine. Improvements were even noted in subjects with near-normal lipid values.

A recent randomized double-blind placebo-controlled study was conducted in order to judge the effect of soy on insulin resistance, glycemic control, and cardiovascular risk markers in post-menopausal women with type 2 diabetes. Thirty-two women with diet-controlled type 2 DM were enrolled and studied for 12 weeks in a crossover design, separated by a 2 week washout period. Statistically lower mean values were found during the soy period for fasting insulin, insulin resistance, total and LDL cholesterol, leading the authors to conclude that soy phytoestrogens may favorably improve the cardiovascular risk profile in diabetic women.

**Fish oil**

An excellent source of anti-inflammatory omega-3 fatty acids eicosapentanoic acid (EPA) and docosahexanoic acid (DHA), fish oil supplements are currently being widely used for both cardiovascular prevention and treatment. Fish oil has also been the subject of active research in relation to diabetes as well. A study in diabetic rats found positive effects on nerve conduction velocity, perhaps pointing to a future use in prevention of human neuropathy. A systematic review evaluating 18 trials published prior to 1998, including 823 diabetic subjects followed for a mean of 12 weeks, demonstrated statistically significant lowering of triglycerides and LDL, but no significant effect on fasting glucose, HgA1C, total cholesterol, or HDL. A recently published study examined prospectively the association between intake of fish and omega-3 fatty acids and risk of coronary heart disease and total mortality among 5,103 female nurses with diagnosed type 2 diabetes but free of cardiovascular disease. Higher consumption of omega-3 fatty acids was associated with a trend toward lower incidence of CHD and total mortality, with the lowest relative risk found among those eating fish 5 or more times per week. This study evaluated fish consumption rather than fish oil supplements. Though its safety and tolerability profile is excellent and preliminary evidence is intriguing, no consensus optimal dosing has been determined for fish oil supplements in diabetic patients.

**BOTANICAL MEDICINES**

**Ginseng (Panax quinquefolius and P. ginseng)**

These adaptogenic herbs have been demonstrated to have hypoglycemic effects in diabetic rat models. Possible mechanisms of action include decreased rate of carbohydrate absorption into the portal hepatic circulation, increased glucose transport and uptake mediated by nitric oxide, increased glycogen storage, and modulation of insulin secretion. The best human clinical trials have investigated American ginseng (P. quinquefolius). A preliminary short-term study found American ginseng to reduce postprandial glyceamia in both type 2 diabetics and nondiabetics. These results may indicate that it is best given before or with meals for full effect. An 8-week trial from the same research group reported decreases in fasting blood glucose and HgA1C.

**Fenugreek (Trigonella foenum-graecum)**

Fenugreek is a legume extensively cultivated in the Middle East, India, and Mediterranean countries. The seeds are a common food spice and have been traditionally used in Ayurveda for their nutritive and hypoglycemic effects. Proposed mechanism of antidiabetic
action are primarily attributed to high fiber content of the seeds and the presence of 4-hydroxyisoleucine, which stimulates insulin secretion. The hypoglycemic effects of fenugreek have been displayed in both animal and human studies. The addition of fenugreek seed to the diet of diabetic rats also normalized free radical metabolism. Most of the human studies are uncontrolled, open label trials. In a recent randomized double-blind placebo-controlled trial, 25 newly diagnosed type 2 diabetics were randomized to receive 1 gm/day of hydroalcoholic extract of fenugreek seeds or placebo capsules for 2 months. Results were statistically significant lowering of area under the curve for blood glucose and insulin, decrease in percent beta-cell secretion, increase in percent insulin sensitivity, decrease in serum triglycerides, and increase in HDL cholesterol. Higher doses of fenugreek may lead to flatulence or diarrhea.

**Bitter melon (Momordica charantia)**

Bitter melon unripe fruit and seeds are used in India, Asia, South America and Africa for the treatment of diabetes. Active components are thought to be charantin, vicine, and polypeptide-p, an insulin-like protein similar to bovine insulin. Hypothesized mechanisms of action include increased insulin secretion, increased glucose oxidation, and decreased hepatic gluconeogenesis. Much of the research on bitter melon is from India and randomized placebo-controlled trials are lacking. An open trial noted improvement in 73% of type 2 diabetics given 2 ounces of juice, while another of 100 diabetic subjects found reduced fasting and postprandial serum glucose levels in 86 patients after drinking an aqueous homogenized suspension of the vegetable pulp. A recently published review acknowledged that hypoglycemic effects may be additive when taken with other glucose-lowering medications, with serious adverse effects of hypoglycemic coma and seizures in children noted. The authors conclude that randomized, placebo-controlled trials are needed to properly assess both safety and efficacy.

**Glucomannan**

Glucomannan is a dietary fiber derived from the tubers of *Amorphophallus konjac*. When placed in water, glucomannan can swell to 17 times its original volume. In Japan, konjac flour is used to make an edible jelly called konyaku. Glucomannan is differentiated from other soluble fibers by its high viscosity in solution. Administration of 4-5 gm with meals can slow carbohydrate absorption and dampen postprandial insulin response by up to 50%. A recently published randomized double-blind crossover clinical trial evaluated the effects of glucomannan supplementation over 28 days on blood lipid and glucose levels in hyperlipidemic type 2 diabetic patients. Among the 22 enrolled subjects, significant reductions were noted in plasma cholesterol (11%), LDL (20%), apoB (13%), and fasting glucose (23%). Earlier studies showed similar effect, raising the possibility for therapeutic potential of glucomannan in the treatment of insulin resistance syndrome.

**Psyllium**

For patients who find reaching the target of 50 grams of fiber daily with diet alone difficult, psyllium husk as a supplement can be a useful adjunct. Placebo-controlled and crossover studies to date have shown psyllium, administered twice daily, to improve post-prandial glucose levels in the range of 10-20%. Fasting blood glucose can also be lowered with regular psyllium supplementation. Lipid profiles improve as well, with reductions on the order of 9% in total cholesterol and 13% in LDL. Psyllium has no significant adverse effects other than the potential for causing constipation if water intake is not adequate; a typical dose is 5 grams twice daily.

**Aloe vera**

Though native to Northern Africa, *aloe vera* has been used throughout the world for its medicinal properties. Its most widespread uses are as a topical gel for burns and to aid wound healing. Hypoglycemic activity has been demonstrated in animal studies of experimentally induces diabetic mice and rats. Two human trials from the same investigative team suggest that aloe gel can improve glycemic control in diabetics. A single-blind, placebo-controlled trial of 72 diabetics over 2 weeks showed improved blood sugar control. A second study evaluated the benefits of aloe in 36 diabetics who failed to respond to the oral medication glibenclamide, showing improvement in those taking glibenclamide plus aloe versus those taking the medication plus placebo. Large double blind studies are needed to further investigate aloe as a treatment for diabetes.

**Nopal (Opuntia streptacantha)**

The nopal, or prickly pear cactus, has been historically used in traditional Mexican medicine for glucose control. Much of the current research into this valuable plant is from Mexico, most studies are available in Spanish. Nopal’s hypoglycemic actions may arise from its high soluble fiber and pectin content, which may affect intestinal glucose uptake. A multiple arm study of 32 type 2 diabetics demonstrated a hypoglycemic effect for stems. A later study by the same researchers employed 14 healthy subjects and 14 diabetics, attempting to assess if the previously described hypoglycemic effect noted in diabetics would be evident in healthy subjects. Following ingestion of 500 g of stems, hypoglycemic activity was not found in healthy subjects, but again was noted in diabetics. Both of these studies indicate that nopal stems may be an effective diabetic treatment, but well-designed double-blind placebo-control trials are lacking.

**Gymnema (Gymnema sylvestre)**

Gymnema is another traditional Ayurvedic herbal diabetes treatment. The plant is endemic to central and southern India. When placed on the tongue, gymnema blocks the taste of sweetness, explaining its Hindi name “gurmar”, or “destroyer of sugar”. Hypoglycemic activity has been demonstrated in both in vitro and animal studies. A study of streptozocin-diabetic rats given GS4 (a water solubilized gymnema extract) for 20 days found that pancreatic beta cells were doubled, while fasting blood glucose decreased to near normal levels. The same investigators simultaneously published an open trial of 22 type 2 diabetics previously taking conventional oral hypoglycemic medication supplemented with 400 mg/d of GS4 for 12–18 months. All patients were found to have a significant reduction in blood glucose, HgA1C, and glycosylated proteins, with 5 patients able to discontinue their oral medication and continue gymnema alone. Elevated insulin levels were also noted in all patients. These researchers speculated that gymnema may function by helping to repair or generate the endocrine pancreas. Similar positive effects were noted in a single small study of type 1 diabetics. Gymnema is well-tolerated and has an excellent safety profile.
3. nutritional counseling should include an emphasis on fiber, whole grains, a healthy balance of saturated to monounsaturated fat, regular physical activity, is critical. 2. When a diagnosis of Type 2 DM is made, a trial of diet and lifestyle intervention is a reasonable first step. If a patient is symptom-free, one would think that a clear connection between mind-body therapies for stress reduction and glycemic control in type 2 diabetes would have been clearly established. 20. A small open trial from Germany showed reduction in hemorrhages and improvement in hyperglycemia in response to oral glucose challenge after 40 days of yoga therapy.99 Qi Gong training has also shown promise.100

Summary of Integrative Treatment Recommendations

1. Any patient at high risk for diabetes based on family history should be counseled regarding the importance of a high fiber, whole grain, low glycemic load diet, as well as regular physical activity and exercise. 2. When a diagnosis of Type 2 DM is made, a trial of diet and lifestyle intervention is a reasonable first step. If a patient is symptom-free, one would think that a clear connection between mind-body therapies for stress reduction and glycemic control in type 2 diabetes would have been clearly established. 20. A small open trial from Germany showed reduction in hemorrhages and improvement in hyperglycemia in response to oral glucose challenge after 40 days of yoga therapy.99 Qi Gong training has also shown promise.100

Mind/Body Approaches

With all that is known at this point regarding the impact of stress on the HPA axis, cortisol production, and neuroendocrine signalling, one would think that a clear connection between mind-body therapies for stress reduction and glycemic control in type 2 diabetes would have been clearly established. To date however the literature on the impact of mind-body approaches on diabetes is sketchy and equivocal. Small studies of relaxation training, some with EMG biofeedback,96,97 and of cognitive-behavioral therapy98 have so far failed to establish a significant impact on glycemic control despite a demonstrable positive effect on anxiety level. One non-controlled study of yoga for diabetes (n=149) did demonstrate a significant improvement in hyperglycemia in response to oral glucose challenge after 40 days of yoga therapy.99 Qi Gong training has also shown promise.100

Bilberry (Vaccinium myrtillus)

Like its American relatives cranberry and blueberry, the European bilberry fruit is rich in powerful anthocyanoside flavonoid antioxidants. Extracts containing anthocyanosides have been shown to stabilize collagen fibers and promote collagen biosynthesis, as well as decrease capillary permeability and fragility.93 Bilberry leaf decoctions have a long history of folk use in Europe for diabetes, though no human studies have been conducted for this purpose. The main current uses of Bilberry extract relate to ophthalmologic disorders, including diabetic retinopathy.94 One double-blind, placebo-controlled trial showed improvement in physical signs of retinopathy and a small open trial from Germany showed reduction in hemorrhages and vascular permeability.95 These trials and animal studies have been performed using preparations standardized to contain 25% anthocyanidins.

Conclusion

The integrative approach to type II diabetes greatly expands the options available to both patient and physician in treating this common metabolic disorder. Even when medications and/or insulin are required, incorporating a knowledge of the role of diet, exercise, mind-body approaches, botanical medicines and nutritional supplements can both potentially decrease the number of medications needed to treat the diabetes, and increase the sense of control the patient has over the course of the illness.

References

Integrative Approach to the Management of Type 2 Diabetes Mellitus


