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Review Article

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Present and Future Preventive Strategies of Diabetes Mellitus by Herbal and Alternative Therapy

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ABSTRACT

Medical plants play an important role in the management of diabetes mellitus especially in developing countries where resources are meager. Before the advent of insulin injections and other pharmaceutical preparations, healers relied heavily upon herbs to treat diabetes. Although numerous herbs are reported to possess some degree of antidiabetic activity, a significant amount of research, as well as traditional usage, suggests that gurmar leaf (*Gymnema sylvestre*), bitter gourd fruit (*Momordica charantia*), and fenugreek seeds (*Trigonella foenum graecum*) may be among the best in terms of efficacy and safety. Type 2 diabetes is a chronic metabolic disease that has a significant impact on the health, quality of life, and life expectancy of patients, as well as on the health care system. Exercise, diet, and weight control continue to be essential and effective means of improving glucose homeostasis. However, lifestyle management measures may be insufficient or patient compliance difficult, rendering conventional drug therapies (i.e., oral glucose lowering agents and insulin injection) necessary in many patients. In addition to adverse effects, drug treatments are not always satisfactory in maintaining euglycemia and avoiding late stage diabetic complications. As an alternative approach, medicinal herbs with antihyperglycemic activities are increasingly sought by diabetic patients and health care professionals. Commonly used herbs for herbal therapy and other alternative therapies, less likely to have the side effects of conventional approaches for type 2 diabetes.

Key words: Diabetes Mellitus, alternative approaches, mineral herbs, acupuncture and hydrotherapy, stem cell therapy

INTRODUCTION

Diabetes is a chronic disease characterized by elevated blood glucose levels and disturbances in carbohydrate, fat and protein metabolism. These metabolic abnormalities result in part from a deficiency of the blood sugar-lowering hormone insulin or from "insulin resistance". It is a serious chronic metabolic disorder that has a significant impact on the health, quality of life, and life expectancy of patients, as well as on the health care system. Diabetes mellitus was first described in ancient Egypt. Aretaeus named it in the 1st century AD. Galenus spoke of diabetes in the 2nd century and blamed it on "kidney weakness."

It is a chronic disorder of carbohydrate, fat and protein metabolism characterized by fasting elevations of blood sugar (glucose) levels and a greatly increased risk of heart disease, stroke, kidney disease, and loss of nerve function. Diabetes can occur when the pancreas does not secrete enough insulin, or if the cells of the body become resistant to insulin; hence, the blood sugar cannot get into the cells which then leads to serious complications. In developing countries its incidence is steadily increasing due to rapid changes in lifestyle. It is a heterogenous disorder and both environmental and genetic factors work in tandem in its pathogenesis. The impaired glucose homeostasis is the result of a dynamic interaction between insulin secretion and insulin action.1 Lifestyle alterations such as modification in diet, patient education and regular physical activity remain important in the management of diabetes.

Classification:

Diabetes is divided into two major categories: type I and type II. Type I or Insulin Dependent Diabetes Mellitus (IDDM) occurs most often in children and adolescents. Type II or Non-Insulin Dependent Diabetes Mellitus (NIDDM) usually has an onset after 40 years of age.

Insulin-Dependent Diabetes Mellitus (IDDM): IDDM is associated with complete destruction of the beta-cells of the pancreas which manufacture the hormone insulin. IDDM patients require lifelong insulin for the control of blood sugar levels. In type 1 diabetes, the pancreas undergoes an autoimmune attack by the body itself, and is rendered incapable of making insulin. Abnormal antibodies have been found in the majority of patients with type 1 diabetes. Antibodies are proteins in the blood that are part of the body's immune system. The patient with type 1 diabetes must rely on insulin medication for survival. In this type I diabetic must learn how to manage his or her blood sugar levels on a day-by-day basis, modifying insulin types and dosage schedules as necessary, according to the results of regular blood sugar testing. About 10% of all diabetics are type I.

Non-Insulin Dependent Diabetes Mellitus (NIDDM): Type 2 diabetes was also referred to as non-insulin dependent diabetes mellitus **(NIDDM)**, or adult onset diabetes mellitus **(AODM)**. In type 2 diabetes, patients can still produce insulin, but do so relatively inadequately for their body's needs, particularly in the face of insulin resistance as discussed above. In many cases this actually means the pancreas produces larger than normal quantities of insulin. A major feature of type 2 diabetes is a lack of sensitivity to insulin by the cells of the body (particularly fat and muscle cells). About 90% of all diabetics are type II. Insulin levels are typically elevated indicating a loss of sensitivity to insulin by the cells of the body. Obesity is a major contributing factor to this loss of insulin sensitivity, with approxi-

mately 90% of individuals with type II diabetes being obese.

Diabetes Insipidus: Diabetes insipidus is caused by the inability of the kidneys to conserve water, which leads to frequent urination and pronounced thirst.

Causes, incidence, and risk factors:

Diabetes insipidus is an uncommon condition that occurs when the kidneys are unable to conserve water as they perform their function of filtering blood. The amount of water conserved is controlled by antidiuretic hormone (ADH, also called vasopressin). ADH is a hormone produced in a region of the brain called the hypothalamus. It is then stored and released from the pituitary gland, a small gland at the base of the brain. Diabetes insipidus caused by a lack of ADH is called central diabetes insipidus. When diabetes insipidus is caused by failure of the kidneys to respond to ADH, the condition is called nephrogenic diabetes insipidus. The major symptoms of diabetes insipidus are excessive urination and extreme thirst. The sensation of thirst stimulates patients to drink large amounts of water to compensate for water lost in the urine. Central diabetes insipidus is caused by damage to the hypothalamus or pituitary gland as a result of surgery, infection, tumor, or head injury. Although rare, central diabetes insipidus is more common than nephrogenic diabetes insipidus. Nephrogenic diabetes insipidus involves a defect in the parts of the kidneys that reabsorb water back into the bloodstream. It occurs less often than central diabetes insipidus. Nephrogenic diabetes insipidus may occur as an inherited disorder in which male children receive the abnormal gene that causes the disease on the X chromosome from their mothers. Nephrogenic diabetes insipidus may also be caused by diseases of the kidney (for example, polycystic kidney disease) and the effects of certain drugs (for example, lithium, amphotericin B, demeclocycline).

Other Types of Diabetes: Other types of diabetes include: secondary diabetes (a form of diabetes that is secondary to certain conditions and syndromes such as pancreatic disease, hormone disturbances, drugs, and malnutrition); gestational diabetes (refers to glucose intolerance occurring during pregnancy); and impaired glucose tolerance (a condition that includes prediabetic, chemical, latent, borderline, subclinical and asymptomatic diabetes). Individuals with impaired glucose tolerance have blood glucose levels and GTT that are intermediate between normal and those that are clearly abnormal. In addition, many practitioners consider reactive hypoglycemia as a prediabetic condition.

Diagnosis:

Fasting Blood Glucose Level:

The standard method of diagnosing diabetes involves the measurement of blood glucose levels. The normal fasting blood glucose level is between 70 and 105 mg/dl. A fasting blood glucose measurement greater than 140 mg/dl on two separate occasions is diagnostic of diabetes. Levels below 50mg/dl indicate fasting hypoglycemia.

The Glucose Tolerance Test:

A more functional test of blood sugar control is the oral glucose tolerance test (GTT). The GTT is a very sensitive test for DM. However, it is also very stressful to the patient and has a relatively low specificity. The National Diabetes Data Group recommends giving a 75 gram glucose dose, dissolved in 300 mL of water, for adults (1.75 g/kg ideal body weight for children) after an overnight fast in subjects who have been consuming at least 150 grams of carbohydrate daily for three days prior to the test. The patient is considered normal if the two hour plasma glucose is less than 140 mg/dl and no value exceeds 200 mg/dl. A confirmatory diagnosis of DM requires that plasma levels be above 200 mg/dl at both two hours and at least once between zero time and two hours.

The Glucose-Insulin Tolerance Test:

Relying on blood sugar levels alone is often not adequate in diagnosing blood sugar disorders. Several studies have shown that the glucose-insulin tolerance test (G-ITT) is more sensitive in the diagnosis of both hypoglycemia and diabetes than the standard GTT. The G-ITT uses a standard 6 hour glucose tolerance test coupled with measurements of insulin levels. The G-ITT appears to be one of the best diagnostic indicators for faulty sugar metabolism. As many as two-thirds of subjects with suspected diabetes or hypoglycemia that have normal glucose tolerance tests will demonstrate abnormal insulin tolerance tests.

Causes of Diabetes:

Hereditary or Inherited Traits: It is strongly believed that due to some genes which passes from one generation to another, a person can inherit diabetes. It depends upon closeness of blood relationship as mother is diabetic, the risk is 2 to 3%, father is diabetic, the risk is more than the previous case and if both the parents are diabetic, the child has much greater risk for diabetes.

Age: Increased age is a factor which gives more possibility than in younger age. This disease may occur at any age, but 80% of cases occur after 50 year, incidences increase with the age factor.

Poor Diet (Malnutrition Related Diabetes): Improper nutrition, low protein and fiber intake, high intake of refined products are the expected reasons for developing diabetes.

Obesity and Fat Distribution: Being overweight means increased insulin resistance, that is if body fat is more than 30%, BMI 25+, waist grith 35 inches in women or 40 inches in males.

Sedentary Lifestyle: People with sedentary lifestyle are more prone to diabetes, when compared to those who exercise thrice a week, are at low risk of falling prey to diabetes.

Stress: Either physical injury or emotional disturbance is frequently blamed as the initial cause of the disease. Any disturbance in Cortiosteroid or ACTH therapy may lead to clinical signs of the disease.

Drug Induced: Clozapine (Clozaril), olanzapine (Zyprexa), risperidone (Risperdal), quetiapine (Seroquel) and ziprasidone (Geodon) are known to induce this lethal disease.

Infection: Some of the strephylococci is suppose to be responsible factor for infection in pancreas.

Sex: Diabetes is commonly seen in elderly especially males but, strongly in women and those females with multiple pregnancy or suffering from (PCOS) Polycystic Ovarian Syndrome.

Hypertension: It had been reported in many studies that there is direct relation between high systolic pressure and diabetes.

Serum lipids and lipoproteins: High triglyceride and cholesterol level in the blood is related to high blood sugars, in some cases it has been studied that risk is involved even with low HDL levels in circulating blood.

What doesn't cause Diabetes:

It's important to also be aware of the different myths that over the years have arisen about the causes of diabetes. Eating sweets or the wrong kind of food does not cause diabetes. However, it may cause obesity and this is associated with people developing Type 2 diabetes. Stress does not cause diabetes, although it may be a trigger for the body turning on itself as in the case of Type 1 diabetes. It does,

however, make the symptoms worse for those who already have diabetes. Diabetes is not contagious. Someone with diabetes cannot pass it on to anyone else.

Diabetes Management:

The primary goal in the management of diabetes is to control blood sugar levels. In the Type I diabetic, this requires regular insulin injections. When blood homeostasis is not maintained, pathological complications begin to manifest. Because diabetics are also at a greater risk of developing cardiovascular disease compared to non-diabetics, preventive measures that include dietary and lifestyle modifications are also important. Fundamental to the successful management of Type II diabetes is dietary modification including the strict control of simple carbohydrate intake and increasing the percentage of complex carbohydrates, as well as fiber. Also important is regular exercise and weight reduction (in overweight individuals). While some cases of Type II diabetes can be controlled by weight loss and diet alone, in some instances the use of insulin or oral hypoglycemic drugs, such as sulphonylureas and biguanidines, are necessary to help keep blood glucose at a normal level. Additionally, dietary supplements such as chromium, may provide benefit to diabetic individuals. The benefits of vitamin E, magnesium, and other nutrients are still being elucidated [1] [2] [3].

In recent years, several plant extracts have been examined for antidiabetic activity in an effort to identify alternative treatment strategies that pose less of a risk for diabetics. Although herbs can be very effective in helping to manage elevated blood glucose, they should not be used in place of insulin in persons with Type I or Type II diabetes requiring insulin.

Herbal Support for Diabetes Management:

Before the advent of insulin injections and other pharmaceutical preparations, healers relied heavily upon herbs to treat diabetes. Although numerous herbs are reported to possess some degree of antidiabetic activity [4], a significant amount of research, as well as traditional usage, suggests that gurmar leaf (*Gymnema sylvestre*), bitter gourd fruit (*Momordica charantia*), and fenugreek seeds (*Trigonella foenum graecum*) may be among the best in terms of efficacy and safety. These, as well as several other valuable herbs such as garlic and ginseng represent safe, useful adjuncts to conventional therapeutic approaches to diabetes management. Also, it is plausible that the insulin and glucose normalizing effects of some of these herbs may benefit the non-diabetic with insulin resistance; however, research in this area is needed. It is important to note that as with any change of diet, medication, or lifestyle with the diabetic, the administration of herbal supplements requires close monitoring of blood glucose levels, as these agents may reduce requirement for insulin or oral hypoglycemic drugs, and may cause hypoglycemia in some individuals.

Conventional Approach to Diet Therapy:

Given the heterogeneous nature of type 2 diabetes, no single dietary approach is appropriate for all patients. Meal plans and diet modifications are generally individualized by a registered dietitian to meet patient needs and lifestyle. A typical conventional approach would recommend a diet composed of 60-65 percent carbohydrate, 25- 35 percent fat, and 10-20 percent protein, with limited or no alcohol consumption [5].

Alternative Approaches:

Alternative therapies with anti-diabetic activity have been researched relatively extensively, particularly in India. Ideal therapies should have a similar degree of efficacy without the troublesome side effects associated with conventional treatments. Alternative treatments for diabetes have become increasingly popular the last several years [6], including medicinal herbs, nutritional supplementation, acupuncture, and hot tub therapy.

Medicinal Herbs:

Many conventional drugs have been derived from prototypic molecules in medicinal plants. Metformin exemplifies an efficacious oral glucose-lowering agent. Its development was based on the use of *Galega officinalis* to treat diabetes [7]. *Galega officinalis* is rich in guanidine, the hypoglycemic component [8]. Because guanidine is too toxic for clinical use, the alkyl biguanides synthalin A and synthalin B were introduced as oral anti-diabetic agents in Europe in the 1920s but were discontinued after insulin became more widely available. However, experience with guanidine and biguanides prompted the development of metformin. To date, over 400 traditional plant treatments for diabetes have been reported, although only a small number of these have received scientific and medical evaluation to assess their efficacy. The hypoglycemic effect of some herbal extracts has been confirmed in human and animal models of type 2 diabetes. The World Health Organization Expert Committee on diabetes has recommended that traditional medicinal herbs be further investigated [9] [10]. The following is a summary of several of the most studied and commonly used medicinal herbs.

Mineral Supplementation:

The treatment of diabetes requires nutritional supplementation, as these patients have a greatly increased need for many nutrients. Supplying the diabetic with additional key nutrients has been shown to improve blood sugar control as well as help prevent or ameliorate many major complications of diabetes.

Chromium:

Chromium is an essential micronutrient for humans. Considerable experimental and epidemiological evidence now indicates that chromium levels are a major determinant of insulin sensitivity, as it functions as a cofactor in all insulin- regulating activities [11]. Chromium facilitates insulin binding and subsequent uptake of glucose into the cell. Supplemental chromium has been shown to decrease fasting glucose levels, improve glucose tolerance, lower insulin levels, and decrease total cholesterol and triglycerides, while increasing HDL cholesterol in normal, elderly, and type 2 diabetic subjects [12] [13]. Without chromium, insulin's action is blocked and glucose levels are elevated. Chromium picolinate, a trivalent chromium (Cr^{3+}), is one of the forms of chromium that exhibits biological activity [14]. A large clinical study on 180 diabetic patients documents the benefit of chromium picolinate for type 2 diabetic patients. In the study, while patients continued their normal medication, they were placed in one of three groups: placebo group, 100mcg chromium picolinate twice daily, or 500mcg chromium picolinate twice daily. There were significant doseand time-dependent decreases in glycosylated hemoglobin, fasting glucose, two-hour postprandial glucose levels, fasting and two-hour postprandial insulin values, and total cholesterol, particularly in the 500 mcg twice daily group[15]. However, not all studies on chromium have yielded positive results. In a controlled six-month study to determine the effect of 200 mcg/day chromium picolinate on individuals with type 2 diabetes, Lee and Reasner reported a decrease in triglycerides but no statistical difference between control and chromium- treated subjects with respect to measured parameters of glucose control [16]. This dosage is considerably smaller than that found effective at lowering glucose in other studies so may explain the

disparate findings among studies. Although no recommended daily allowance (RDA) has been established for chromium, over 200mcg/ day appears necessary for optimal blood sugar regulation. A good supply of chromium is assured by supplemental chromium in addition to dietary sources. Good dietary sources are brewer's yeast63 and barley flour [17], while refined sugars, white flour products, and lack of exercise can deplete chromium levels. Trivalent chromium has long been considered to be a safe nutritional supplement [18]. Although the hexavalent form of chromium is a known human respiratory tract carcinogen when inhaled in high-exposure industrial settings, there is no evidence of any carcinogenesis in humans from the trivalent form of chromium found in chromium supplements [19] [20]. Further evaluation of the safety and efficacy of trivalent chromium in diabetes treatment may be warranted.

Vanadium:

Prior to the discovery of insulin in 1922, vanadium was used for the control of blood sugar. Two small studies (one with six type 2 diabetic patients, one with seven type 2 diabetic patients) have confirmed the effectiveness of vanadyl sulfate at a dose of 100 mg/day in improving insulin sensitivity [21] [22].

Magnesium:

A deficiency of magnesium is significantly more common in type 2 diabetics than in the general population [23]. Magnesium deficiency has been associated with complications of diabetes, retinopathy in particular. One study found patients with the most severe retinopathy were also lowest in magnesium [24].

Physical Interventions:

Acupuncture and Hydrotherapy:

Acupuncture is best known in the United States as an alternative therapy for chronic pain. However, it has been used for the treatment of diabetes and related complications during the past several decades. There are numerous Chinese publications on the use of acupuncture for diabetes, but only those published in English will be cited here. Acupuncture may be effective in treating not only diabetes, but also in preventing and managing complications of the disease [25]. The effects of acupuncture on diabetes have been observed experimentally and clinically [26] [27]. Animal experiments have shown that acupuncture can activate glucose-6-phosphatase (an important enzyme in carbohydrate metabolism) and affect the hypothalamus. Acupuncture can act on the pancreas to enhance insulin synthesis, increase the number of receptors on target cells, and accelerate the utilization of glucose, resulting in lowering of blood sugar. Data from other studies have shown the beneficial anti-obesity effect of acupuncture, which is the most modifiable risk factor for type 2 diabetes. It appears that the therapeutic effect of acupuncture on diabetes is not the result of its action on one single organ, but on multiple systems. Four commonly used points are: (1) Zusanli point, located three inches below the lateral knee depression, one finger width from the lateral side of the anterior crest of the tibia; (2) Sanyinjiao point, located three inches above the tip of the inner ankle, on the posterior margin of the metatarsal bone; (3) Feishu point, located 1.5 inches lateral and inferior to the spinous process of the third thoracic vertebra in a prone position; and (4) Shenshu point, located 1.5 inches lateral to the posterior midline, lateral and inferior to the spinous process of the second lumbar vertebra in a prone position. These acupuncture points were selected based on traditional Chinese medicine theory. During the treatment, other points can be added according to symptoms and signs [25]. Other methods have also been employed such as point injection with normal saline, small dose insulin, and Chinese herbal medicine extracts. Treatment is generally given once daily or once every other day as a course of 14-21 treatments. It is believed that the longer the course of treatment, the more marked will be the effect. Acupuncture can be effective in treating complications of diabetes, often with marked improvement in clinical symptoms. Better therapeutic results are obtained in patients with dietary control than in those without it. Physical exercise, breathing exercises, and massage can help improve the therapeutic effect.

Stem Cell Therapy in Diabetes management:

Both type 1 and type 2 diabetes are characterized by a marked deficit in beta-cell mass causing insufficient insulin secretion. Beta-cell replacement strategies may eventually provide a cure for diabetes. Current therapeutic approaches include pancreas and islet transplantation, but the chronic shortage of donor organs restricts this treatment option to a small proportion of affected patients. Moreover, recent evidence shows a progressive decline in beta-cell function after islet transplantation so that most patients have to revert to insulin treatment within a few years [28].

Diabetes management by Drug Therapy:

Antidiabetic drugs may be subdivided into six groups: insulin, sufonylureas, alpha-glucosidase inhibitors, biguanides, meglitinides, and thiazolidinediones.

Insulin (Humulin, Novolin) is the hormone responsible for glucose utilization. It is effective in both types of diabetes, since, even in insulin resistance, some sensitivity remains and the condition can be treated with larger doses of insulin. Most insulins are now produced by recombinant DNA techniques, and are chemically identical to natural human insulin. Isophane insulin suspension, insulin zinc suspension, and other formulations are intended to extend the duration of insulin action, and permit glucose control over longer periods of time. In 2003, research suggested that inhaled forms of insulin offered advantages to injected types, but further study was needed on its long-term effects on the lungs and cost-effectiveness.

Sulfonylureas (chlorpropamide [Diabinese], tolazamide [Tolinase], glipizide [Glucotrol] and others) act by increasing insulin release from the beta cells of the pancrease. Glimepiride (Amaryl), a member of this class, appears to have a useful secondary action in increasing insulin sensitivity in peripheral cells.

Alpha-glucosidase inhibitors (acarbose [Precose], miglitol [Glyset]) do not enhance insulin secretion. Rather, they inhibit the conversion of disaccharides and complex carbohydrates to glucose. This mechanism does not prevent conversion, but only delays it, reducing the peak blood glucose levels. Alpha-glucosidase inhibitors are useful for either monotherapy or in combination therapy with sulfonylureas or other hypoglycemic agents. Metformin (Glucophage) is the only available member of the biguanide class. Metformin decreases hepatic (liver) glucose production, decreases intestinal absorption of glucose and increases peripheral glucose uptake and use. Metformin may be used as monotherapy (alone), or in combination therapy with a sulfonylurea.

Meglitinide class: repaglinide (Prandin) and nateglitinide (Starlix). The mechanism of action of the meglitinides is to stimulate insulin production. This activity is both dose dependent and dependent on the presence of glucose, so that the drugs have reduced effectiveness in the presence of low blood glucose levels. The meglitinides may be used alone, or in combination with metformin. The manufac-

turer warns that nateglitinide should not be used in combination with other drugs that enhance insulin secretion.

Rosiglitazone (Avandia) and pioglitazone (Actos) are members of the thiazolidinedione class. They act by both reducing glucose production in the liver, and increasing insulin dependent glucose uptake in muscle cells. They do not increase insulin production. These drugs may be used in combination with metformin or a sulfonylurea.

DISCUSSION:

Alternative therapies with antihyperglycemic effects are increasingly sought by patients with diabetes. This comes as no surprise since alternative treatments have been most widely used in chronic diseases, which may be only partially alleviated by conventional treatment. Herbal medications are the most commonly used alternative therapy for blood sugar control; however, their safety and efficacy need to be further evaluated by well-designed, controlled clinical studies. Because various non-standardized forms of the herbs have often been the testing material, the results have been difficult to replicate. Therefore, preparation of standardized medicinal herbs is urgently needed in future studies and therapies. Although herbs used for diabetes are less likely to have the drawbacks of conventional drugs, potential adverse herb-drug interactions should be kept in mind for patients also receiving conventional antidiabetic medications. Several minerals have been found to benefit people with diabetes, either because of potential deficiencies or because of the beneficial effect on glucose metabolism. Among the most important minerals for supplementation are chromium, magnesium, and vanadium. Other potentially beneficial treatments for type 2 diabetes include acupuncture and hydrotherapy.

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