Hypoglycemic effects of *Trigonella foenum-graeucum* (fenugreek) seeds and *Momordica charantia* (karela) juice on patients with Type II diabetes

Ashmi Patel

A. Study Purpose and Rationale

Despite current therapies, diabetes tends to be a poorly controlled disease, with numerous well-known complications, leading to significant morbidity and mortality. The U.K.Prospective Diabetes Study showed that improved glucose control in type II diabetic subjects reduced the incidence and progression of microvascular and likely macrovascular disease. Sulfonylureas and metformin, though valuable treatments, are often unable to lower glucose to within normal range or to reinstate a normal pattern of glucose homeostasis. Thus there exists a need for additional therapeutic adjuncts in type II diabetics.

Renewed attention to alternative medicines has stimulated a new wave of research interest in traditional therapies. The World Health Organization expert committee on diabetes has recommended that traditional methods of treatment of diabetes should be further investigated. A multitude of herbs, seeds, and plant products have been utilized for the treatment of diabetes throughout the world, for many centuries. Antidiabetic plant medicines might provide an important source of new oral hypoglycemic compounds for development as pharmaceutical entities, or as simple dietary adjuncts to existing therapies. Although a botanical substitute for insulin seems unlikely, compounds that stimulate insulin biosynthesis and secretion, or promote peripheral glucose uptake and utilization, are realistic possibilities.

The purpose of this study is to investigate the effects of fenugreek seeds and karela juice in type II diabetic patients. In several animal studies and small human studies, these products show promise to be potential therapeutic agents. Both are widely consumed as food products and as treatments for diabetes, in Asia and Africa. Powdered fenugreek seeds when added to an oral glucose tolerance test solution significantly reduced postprandial glucose levels in experimentally induced diabetic rats (Madar et al) and dogs. Ribes et al showed that fenugreek decreased the levels of glucagon and somatostatin in diabetic dogs. Madar et al gave 15 g of ground fenugreek seeds to 21 patients with type II diabetes and subsequently measured postprandial glucose levels during a meal tolerance test. Postprandial glucose levels were significantly reduced at 30, 60, 120, and 180 minutes when fenugreek was added to the meal, without a significant change in insulin levels. Sharma et al incorporated 25 g of seeds into the meals of 5 type II diabetics for 3 weeks. Glucose tolerance test was performed before and after this 3 week period. Administration of fenugreek produced a significant improvement in fasting and postprandial glucose levels and serum cholesterol levels. Serum insulin levels were decreased after treatment with fenugreek. Sharma et al also incorporated 100g of defatted fenugreek powder into isocaloric diets of 10 type I diabetics for 10 days. The fenugreek diet reduced fasting blood sugar, improved the glucose tolerance test, and serum total cholesterol, LDL, VLDL, and triglycerides, without a change in HDL.

Orally administered Karela extract has also been shown to improve postprandial glucose levels in normal and diabetic mice from 30 minutes to over 3 hours (Day et al). The same study showed that this glucose lowering effect is independent of intestinal glucose absorption and insulin secretion and involves an extrapancreatic effect. Leatherdale et al studied the effect ot karela on glucose and insulin concentrations in 9 type II diabetics. Patients underwent three glucose tolerance tests: a standard test, a test with 50 cc karela juice, and a test after 8-11 weeks of eating karela daily. Karela juice reduced glucose levels, as did the chronic consumption of fried karela, though to a smaller degree. A recent study by Ahmed et al has demonstrated that there was a significant increase in the number of β cells in the pancreas of karela treated diabetic rats when compared to untreated diabetics, without a change in the

number of α cells. In sum, fenugreek seeds and karela juice have been shown to exert significant hypoglycemic activity in studies involving animals and small numbers of humans. Acute consumption within the context of studies and chronic consumption as part of the diet, in various parts of the world, has demonstrated these products to be safe.

B. Study Design and Statistical Analysis

The study will be a randomized, placebo-controlled, double-blinded, clinical trial, with 4 parallel arms. The study will require a total of 100 type II diabetic patients who will be randomly assigned to 4 groups (A-D) of 25 patients. All groups will receive 4 weeks of an isocaloric, control diet, followed by 12 weeks of the diet plus an intervention or diet plus placebo. Group A will receive ground fenugreek seeds plus placebo juice capsules. Group B will receive karela juice capsules plus placebo seeds. Group C will receive both fenugreek seeds and karela juice capsules. Group D will receive placebo seeds and placebo juice capsules. The primary endpoint measured will be hemoglobin A1C. The secondary outcomes will be mean fasting and postprandial glucose levels, as well as a fasting serum cholesterol panel. HgbA1C will be measured at baseline, after the 4 weeks of control diet, and after 12 weeks of intervention. Patients will also measure fasting glucose daily and postprandial (2 hours post breakfast, lunch, and dinner) glucose once a week, during the diet and diet plus intervention period. The mean fasting and postprandial glucoses for each patient will be calculated during each period. The difference in HgbA1C between the post diet and post intervention values will be calculated for each patient. The mean of this difference in each group will be compared to the mean of the difference in the placebo group. Similarly, the change in the mean fasting and postprandial glucose levels will be calculated for each patient. The mean of this change in each group will be compared to the mean of the change in the placebo group. A fasting cholesterol panel will be obtained at baseline, after the 4 week diet period, and after the 12 weeks of intervention period. The change in lipids of each group will be compared to the placebo group, in a fashion similar to that of HgbA1C and serum glucose levels.

The data will be analyzed using the unpaired t-tests. The study requirement of 25 patients per group is based on a power of 80% and a p value of 0.01 for detecting a difference in mean HgbA1C of 1.0%, which would be a clinically relevant outcome.

C. Study Procedures

Patients will receive nutrition counseling on an individual basis to design an isocaloric diet consisting of 50% carbohydrates, 30% fat, and 20% protein. Patients will keep daily records of their food intake and review these data with the nutritionist on a bi-weekly basis. The goals are for each patient to maintain a stable weight and have a similar diet during the diet alone and diet plus intervention phases. Patients will also be instructed to use a One-Touch glucometer to measure fasting and postprandial glucose levels and will record these values. Karela juice will be extracted from fresh karela using a commercial juice extractor, after removal of the seeds. The juice will be concentrated by rotary evaporation to yield a tenfold concentrate. 50 cc's of fresh juice will be concentrated to 5 cc's and subsequently packaged in 2 capsules. 5 cc's of a placebo liquid of similar will be similarly encapsulated. Each patient will receive 2 capsules of the karela juice or the placebo with breakfast, lunch, and dinner. Fenugreek seeds will be defatted to remove their bitterness. 25 grams of ground fenugreek powder, which is odorless and tasteless, will be incorporated into unleavened wheat bread (chapati). Each patient will consume 1 piece of bread with fenugreek or 1 piece of placebo bread, with breakfast, lunch, and dinner.

D. Study Drugs

Fenugreek seeds and karela juice are natural plant products. Both have been consumed chronically as food products and as medicines for centuries throughout India, China, and Africa. Such wide use as well as administration in studies involving animals and humans, has shown them to be well

tolerated and without deleterious effects. Fenugreek has been reported to cause occasional cases of diarrhea and upset stomach.

E. Medical Devices

None

F. Study Questionnaires

None

G. Study Subjects

Eligible patients will be men and women, age 25-75, BMI<35, who have newly diagnosed type II diabetes or are known to have diabetes and are treated with diet alone. Patients in the study should have fasting glucose less than 200 and greater than 126. Patients with ketonuria or patients who are currently taking sulfonylureas, metformin, or insulin will be excluded. Patients who are pregnant or lactating will also be excluded.

H. Recruitment of Subjects

Subjects will be recruited from the Naomi Berrie Diabetes Center and the General Medicine as well as specialty clinics at AIM and ACNC. Flyers with the purpose and inclusion/exclusion criteria will be posted at these clinics. If the patient replies first, their physician will be contacted and informed of the purpose of the study. If the physician consents to the study, the patient will then be consented to participate in the study. The primary physicians will continue to follow their patients as they would have, independent of the study.

I. Confidentiality of Study Data

Patients will be coded by # of entry. Patient's medical information will be kept strictly confidential and will not be divulged without written permission of the patient.

J. Location of Study

The AIM and ACNC clinics of NY Presbyterian Hospital and the Naomi Berrie Diabetes Center.

K. Conflict of Interest

None

L. Potential Risks

There is a low likelihood of diarrhea and stomach upset in patients randomized to receive fenugreek seeds. Though both fenugreek and karela are expected to exert hypoglycemic activity, these treatments may not be as effective as standard treatment. Though it is felt to be of very low likelihood, subjects who receive placebo instead of active treatment, may have progression of any existing complications of diabetes during the 4 month study period.

M. Potential Benefits

The study will likely yield two natural, safe products for the treatment of type II diabetes. These will likely serve as adjuncts to standard therapy and will ultimately provide improved control of diabetes for the study subjects and for society as a whole. Patients will also receive nutrition counseling and instruction of blood glucose monitoring as well as information of the diabetes as a disease, its complications, and how they can be prevented.

N. Alternative Therapies

Sulfonylureas , metformin, and insulin. The risks and benefits of these therapies have been well studied and described.

O. Compensation to Subjects

None

P. Costs to Subjects

None

Q. Minors as Research Subjects

R. Radiation or Radioactive Substances

None

S. References

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