Effect of Pancreas Tonic (an Ayurvedic herbal supplement) in Type 2 Diabetes Mellitus

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Although there is widespread use of herbal dietary supplements that are believed to benefit type 2 diabetes mellitus, few have been proven to do so in properly designed randomized trials; their efficacy for intermediate-term glucose control remains unclear. Pancreas Tonic is a botanical mixture of traditional Indian Ayurvedic herbs currently available as a dietary supplement. We report the results of a single-center, randomized, double-blind, placebo-controlled 3-month trial of Pancreas Tonic in type 2 diabetic patients inadequately treated with diet/lifestyle or stable doses of sulfonylureas and/or metformin for at least 3 months. Patients with type 2 diabetes for ≥ 1 year were entered into 2 strata of hemoglobin A_{1c} (HbA_{1c}) levels (stratum 1: 8.0% to 9.9%; stratum 2: 10.0% to 12.0%). All subjects began a 1-month single-blind placebo run-in phase, followed by randomization in a 2:1 ratio of active treatment: placebo, to 3 months of double-blind treatment with either Pancreas Tonic or matching placebo (2 capsules 3 times a day). Concurrent oral agents were continued unchanged throughout the study. The primary outcome was the change in HbA_{1c} from randomization; results of each stratum were analyzed independently. The baseline characteristics of 36 subjects who completed the study were comparable between treatment groups. Nineteen subjects entered stratum 1 and 17 entered stratum 2. A statistically significant reduction of HbA_{1c} from randomization to end-of-study was seen in the stratum 2 subjects (Pancreas Tonic: 10.1% ± 1.0% to 8.8% ± 1.9%, $P = .004$; placebo: 10.8% ± 1.4% to 11.2% ± 1.8%, not significant [NS]). No significant HbA_{1c} reductions were seen in the stratum 1 subjects. There were no significant treatment-related differences in the fasting plasma glucose (FPG), lipids, body mass index (BMI), body composition, blood pressure, insulin sensitivity estimates using the minimal model, glucose and insulin responses to a meal challenge, quality of life, adverse events, or other safety indices between treatment groups. Pancreas Tonic was well tolerated. Treatment with Pancreas Tonic (2 capsules 3 times per day) for 3 months significantly improved glucose control in type 2 diabetic patients with HbA_{1c} levels between 10.0% to 12.0%. This study represents the first properly designed, prospective intervention trial of therapy with an Ayurvedic herbal supplement for intermediate-term glucose control in type 2 diabetes.

TYPE 2 DIABETES mellitus affects approximately 17 million individuals in the United States.[1] In particular, ethnic minorities, such as African Americans and Hispanic Americans, are affected disproportionately, having a 2-fold to 3-fold higher prevalence of disease compared with age-matched Caucasian patients.[2] Although a growing number of oral pharmacologic options are now available for the management of type 2 diabetes, acting through a variety of mechanisms that confer additive glucose-lowering effects, the effectiveness of such therapies still remains inadequate, as nationwide estimates of hemoglobin A_{1c} (HbA_{1c}) levels seldom reach the recommended target levels of $<7\%$ set by the American Diabetes Association (ADA).[3]

Surveys indicate that the North American public has an avid interest in the potential benefit of complementary and alternative therapies, as evidenced by the widespread use of herbal and "natural" substances and the billions of dollars spent on these supplements annually within the United States.[4,5] While many of these therapies targeted for the treatment of diabetes claim to demonstrate glucose-lowering benefits, very few of these claims have ever been substantiated in a scientifically rigorous fashion with properly conducted, randomized, placebo-controlled trials. Instead, such claims are often based on anecdotal reports, observational analyses, or uncontrolled prospective trials. A recent review of this literature demonstrated the relative paucity of well-designed trials for these therapies, but suggested that several compounds hold potential promise and warranted further study.[6] The US National Institutes of Health (NIH) has emphasized the pressing need for properly designed trials examining the therapeutic potential of complementary and alternative medicines, and an Office of Complementary and Alternative Medicine (CAM) has been established specifically to meet this aim. However, since its inception in 1992, the total number of peer-reviewed publications funded by this effort that have appeared in the medical literature, and the number of controlled clinical trials that are interpretable, have been, to quote the editorial of Angell and Kassirer,[7] "disappointing."

For some 3,000 years, the traditional medical practice of Ayurveda has been used in India and has since found acceptance in other parts of Asia as well as the West. According to folklore, it has therapeutic benefits for numerous conditions, including diabetes mellitus, through a combination of approaches including diet, exercise, herbs, massage, and meditation. The herbal components have been proposed to possess antidiabetic properties and are used either singly or in specified mixtures. One such botanical mixture is currently available in North America as a dietary supplement marketed under the trade names Pancreas Tonic or AntiBetic. A variety of preclin-

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ical studies, using in vitro or in vivo animal models, have suggested that various components of this mixture possess antidiabetic properties. For some of these components, a limited number of small-scale, uncontrolled and/or short-term human studies have suggested that these components may provide glucose-lowering benefits for diabetic patients, although such studies are still largely inconclusive.[8-18]

We now report the results of a single-center, randomized, double-blind, placebo-controlled trial of Pancreas Tonic in type 2 diabetic patients inadequately treated with diet and lifestyle, with or without stable doses of oral antidiabetes agents (sulfonylurea and/or metformin), for a period of 3 months. We believe this to be the first randomized, double-blinded, placebo-controlled clinical trial to evaluate the intermediate-term efficacy for overall glucose control of an Ayurvedic herbal dietary supplement in type 2 diabetes mellitus.

MATERIALS AND METHODS

Subjects

Study subjects were recruited voluntarily from the Diabetes Clinic of Martin Luther King Jr./Charles R. Drew Medical Center, the Hubert Humphrey Comprehensive Health Center, both located in Los Angeles, CA, as well as the community at-large of south Los Angeles. These medical centers serve a large population of low income and low socioeconomic level ethnic minority individuals of largely Hispanic and African American origin. Eligible individuals were required to have a diagnosis of type 2 diabetes mellitus (according to the ADA criteria) for at least 1 year prior to study entry and to have been treated with a stable dose of oral antidiabetes agents, or a stable dietary and lifestyle regimen without pharmacotherapy, for at least 3 months. Subjects also had to be between the ages of 18 and 70 inclusive with HbA_{1c} levels between 8% and 12% inclusive at the time of screening. Diabetic patients treated with insulin were excluded from the study. Other exclusionary criteria included pregnant or lactating women or women planning to become pregnant during the course of the study; use of any investigational drug during or within 30 days prior to screening for the study; any hospitalization or emergency room visits for hyperglycemia within the past 6 months or 2 or more severe hypoglycemic episodes within the past 6 months; a history of recreational drug or alcohol dependence; individuals with clinically significant abnormalities on the baseline electrocardiogram (EKG), a history of myocardial infarction or cerebrovascular accident within the past 6 months, or a coronary revascularization procedure within the past 3 months; a history of a seizure disorder; clinically significant gastroparesis or orthostatic hypotension; congestive heart failure requiring pharmacologic therapy; nephrotic syndrome or serum creatinine $\geq$ 1.4 mg/dL; hepatic disease or hepatic enzyme or bilirubin levels $\geq$ 2 times the upper limit of the normal range; active infections (eg, human immunodeficiency virus [HIV]) or a history of severe infection within 30 days prior to screening; any major surgical procedure within 30 days of screening; any history of malignancy other than basal cell skin carcinoma; clinically significant anemia (defined as a hemoglobin level $<$ 11.0 g/L); or any other circumstances or abnormalities that may interfere with the interpretation of data or completion of the study. Informed consent was obtained in the patient's primary language. The study was conducted on the Clinical Trials Unit of Charles R. Drew University of Medicine and Science, and the study protocol was reviewed and approved by the Institutional Review Board of Charles R. Drew University of Medicine and Science.

Table 1. Composition of Pancreas Tonic

Ingredient	% Dry Weight
Aegle marmelose (leaves)	30
Pterocarpus marsupium (heartwood)	30
Syzigium cumini (fruit)	10
Momordica charantia (seeds)	7
Gymnema sylvestre (leaves)	5
Trigonella foenum graecum (seeds)	5
Azadirachta indica (seeds)	5
Ficus racemosa	5
Tinospora cordifolia (stem)	2
Cinnamomum tamala (leaves)	1

Study Design

This is a single-center, double-blind, placebo-controlled, 3-month outpatient study, with a 1-month run-in period during which subjects received placebo in a single-blind fashion (2 capsules 3 times a day with meals). Upon meeting all entry criteria, subjects were placed into either a lower stratum of HbA_{1c} (8.0% to 9.9%) or a higher stratum (10.0% to 12.0%) and then randomized within each stratum in order to improve the chance that the initial HbA_{1c} level between the active treatment and control groups would be similar. Upon randomization, the active treatment group received Pancreas Tonic capsules and the control group received matching placebo capsules.

Study Medication

Pancreas Tonic is an herbal mixture of 10 herbal extracts. The dry weight composition is listed in Table 1. Capsules of Pancreas Tonic were manufactured by US Botanicals (Bell Gardens, CA). In quality control testing, a randomly selected batch was shown not to contain any sulfonylureas, biguanides, α-glucosidase inhibitors, or thiazolidinediones, as evidenced by high-performance liquid chromatography (HPLC) analyses conducted independently by Ameritech Laboratories (College Point, NY). Assays conducted on 7 different batches of Pancreas Tonic from US Botanicals demonstrated consistent percentage concentrations of each herbal ingredient across these batches, with coefficients of variation for the percent dry weight composition ranging from 1.4% to 7.1% for each of the 10 components of Pancreas Tonic. Placebo capsules were also provided by US Botanicals. There were no perceptible differences in appearance, odor, or taste between active drug- and placebo-containing capsules. Both active drug and matching placebo were taken as 2 capsules 3 times per day with meals.

Study Procedures

Following screening, all eligible subjects were given nutritional and lifestyle counseling by a registered dietitian as they entered into the 1-month single-blind placebo run-in phase prior to randomization. Single-blind placebo capsules during the run-in phase were taken 3 times a day with meals, in the same manner as for the double-blind phase. At screening, a full medical history, physical examination, 12-lead EKG, fasting plasma glucose (FPG) concentration, HbA_{1c} level, fasting lipid profile consisting of a total, high-density lipoprotein (HDL)-cholesterol, calculated low-density lipoprotein (LDL)-cholesterol (by the Friedewald equation[19]) and fasting triglycerides, complete blood count, a full chemistry panel including hepatic transaminase levels and other indices of hepatic function, routine urinalysis, and a pregnancy test for women of childbearing potential, were all obtained. Subjects were instructed on the techniques of self-glucose monitoring for daily fasting and preprandial supper readings, as well as for hypoglycemic symptoms; results were reviewed with the subjects at each visit. Subjects with readings $<$ 100 mg/dL or $>$ 250 mg/dL on 3 or

more readings within a 1-week period during the 1-month placebo run-in period were excluded from the study. After the run-in phase, randomization was performed in a 2:1 ratio of Pancreas Tonic:placebo, using random numerical codes.

Concurrent oral antidiabetes drugs (sulfonylurea and/or metformin) were continued at the same dosage throughout the study and were adjusted only for hypoglycemia (defined as readings by self-glucose monitoring $<$ 100 mg/dL for 3 days in any 1-week period or unexplained symptoms consistent with hypoglycemia). Subjects were seen in follow-up at 2, 4, 8, and 12 weeks following randomization. Clinical assessments at each visit included a review of concomitant medications and adverse events, vital signs, body weight and body mass index (BMI), and a FPG concentration. A dietary assessment, a full physical examination, a diabetes-related quality-of-life questionnaire (a modified SF-36[20]), HbA_{1c} measurement, fasting lipid panel, body composition analysis by bioelectrical impedance analysis (BIA) and analysis using the RJL Cyprus 1.0 software (RJL Systems, Clinton Twp, MI), a meal challenge study, and an insulin-modified frequently-sampled intravenous glucose tolerance test (FSIVGTT) were all conducted at randomization and at the 12-week end-of-study visit. The meal challenge study used a nutrient drink composed of 242 kcal, 41 g carbohydrate, 4.1 g total fat, and 10.2 g total protein, in a single 8-ounce (240 mL) can. (Boost; Mead Johnson, Evansville, IN). Glucose and insulin samples were drawn 15 minutes prior to and at the time of the ingestion of the prescribed study medication dose followed by ingestion (over 5 minutes) of the drink. Blood was then further sampled for glucose and insulin at 30, 60, 90, 120, 180, and 240 minutes after time = 0 minutes. The insulin-modified FSIVGTT used a glucose bolus of 0.3 g/kg body weight and a bolus of Regular Human Insulin (0.05 U/kg body weight) (Humulin R; Eli Lilly, Indianapolis, IN) 20 minutes later; analysis used the Bergman Minimal Model (MinMod v.3.0).[21]

A 12-lead EKG was repeated at the end-of-study visit. Complete blood counts, full chemistry panels including indices of hepatic function, and routine urinalyses were measured monthly during the double-blind phase. Urine pregnancy tests were conducted at randomization and after 2 months of double-blind treatment for all women of childbearing potential.

Outcome Indices

The primary study outcome was the change in HbA_{1c} from the time of randomization. Secondary outcomes included changes in FPG, lipid and lipoprotein parameters, blood pressure, BMI, body composition by BIA (total fat and fat-free mass), general hematologic and biochemical parameters (including hepatic transaminases and urinalyses), and changes on the 12-lead EKG. Changes of insulin sensitivity (S_i), glucose effectiveness (S_g), acute (first-phase) insulin response to intravenous glucose (AIR_g, defined as the first 10 minutes after the glucose bolus), and the disposition index (DI, defined as the product of S_i and AIR_g) were obtained from the FSIVGTT using the Bergman Minimal Model. Changes in the glucose and insulin areas under the curve (AUC) above the baseline values were obtained for the meal challenge tests using the trapezoidal method, with baseline values defined as the average of the -15 and 0 minute measurements. For all AUC calculations with missing insulin or glucose values at the end of the procedure, the last available value was extrapolated for the remainder of the procedure. For AUC calculations with missing values in the middle of the procedure, the average of the flanking values were used in their absence.

Withdrawals

Subjects were withdrawn from the study if: (1) their HbA_{1c} level exceeded 12.0% at any time during the study, (2) self-glucose monitoring revealed levels $>$ 300 mg/dL for 3 days in any 1-week period, (3) the subject developed polyuria or polydipsia, (4) hepatic transaminase levels exceeded 3 times the upper limit of the laboratory normal range (ULN), (5) hemoglobin levels decreased by a decrement of at least 1 g/dL, (6) serum creatinine increased by an increment of at least 0.5 mg/dL, (7) any other adverse event warranted discontinuation from the study for safety reasons as judged by the investigators, or (8) compliance with study procedures, scheduled visits, or the proper use of the study medication was consistently shown to be poor.

Laboratory Analyses

General chemistry, hematology and urinalysis panels, including FPG, fasting lipid panels and HbA_{1c} levels were performed by the King/Drew Medical Center clinical laboratories using standard methodologies. HbA_{1c} was measured by an HPLC assay with a normal range of up to 6.2%. Insulin levels were assayed using a human insulin-specific radioimmunoassay that has $<$0.2% cross reactivity with human proinsulin, according to the manufacturer's protocol (Human Specific Insulin RIA Kit; Linco, St Charles, MO).

Statistical Analyses

Baseline characteristics were compared among the 2 treatment groups and the dropout subjects. Continuous variables were tested using 1-way analysis of variance (ANOVA) followed by pair-wise comparisons with Student's *t* test only if ANOVA was significant; categorical variables were tested with chi-square tests. The primary outcome variable, the change in HbA_{1c} levels from randomization to end-of-study, was analyzed in each stratum of entry HbA_{1c} levels using paired Student's *t* tests for changes within each group. Changes in FPG were analyzed by ANOVA of repeated measures; changes between randomization and end-of-study in all other variables were analyzed using paired Student's *t* test for the placebo and active treatment groups, similar to HbA_{1c}.

The authors were solely responsible for the design, conduct, data collection, statistical analyses, and data interpretation. The study sponsor played no role in these functions, the data were not reported to the study sponsor, and the study sponsor played no role in dictating whether or where this study would be submitted for publication.

RESULTS

Baseline Characteristics

The entry characteristics of the study subjects are shown in Table 2. Of 85 patients screened over a 2.5-year period, 63 subjects met the entry criteria (Fig 1). Forty-seven subjects were randomized following a successful single-blind run-in period. Of these, 36 successfully completed the study, encompassing 19 subjects in stratum 1 and 17 subjects in stratum 2 (Fig 1). Of the 27 subjects who failed to complete the study, 16 dropped out prior to randomization. Of the remaining 11 subjects who dropped out after randomization, 3 and 8 were from the placebo and Pancreas Tonic arms, respectively, consistent with the overall 2:1 randomization ratio of Pancreas Tonic to placebo. Overall, 13 of the 27 subjects were withdrawn because of noncompliance with study procedures (only 5 of whom were randomized prior to withdrawal; 1 of 3 assigned to placebo, and 4 of 8 assigned to Pancreas Tonic, which was not incongruent with our 2:1 randomization ratio), 7 subjects withdrew because of relocation or conflicts with work schedules, 4 subjects were withdrawn prior to randomization because of glycemic control increasing beyond the allowable limits of the study, 2 subjects were hospitalized while receiving single-blind placebo (1 subject had a seizure, 1 subject fell) and opted to discontinue, and 1 subject was withdrawn because of angina exacerbation. This

Table 2. Entry Characteristics of Study Subjects

	Placebo	Pancreas Tonic	Dropouts
n	13	23	27
Age (yr)	47.4 ± 7.0	47.6 ± 11.5	51.1 ± 7.6
Male/female	4/9	6/17	11/16
African American (no.)	4	2	5
Hispanic (no.)	8	20	21
Caucasian (no.)	1	0	1
Asian (no.)	0	1	0
Duration of diabetes (yr)	4.3 ± 3.1	3.9 ± 3.2	5.2 ± 5.0
Dietary/lifestyle therapy only (no.)	1	5	7
Sulfonylurea monotherapy (no.)	5	5	8
Metformin monotherapy (no.)	1	4	3
Combination therapy (no.)	6	9	9
BMI (kg/m^2)	34.8 ± 9.7	31.4 ± 5.7	31.7 ± 6.7
HbA_{1c} (%)	9.9 ± 1.7	9.8 ± 1.3	10.1 ± 1.4
Fasting plasma glucose (mg/dL)	211 ± 62	227 ± 55	222 ± 64
Systolic blood pressure (mm Hg)	125 ± 17	123 ± 12	134 ± 16*
Diastolic blood pressure (mm Hg)	73 ± 10	70 ± 12	76 ± 11
Total cholesterol (mg/dL)	193 ± 34	193 ± 35	214 ± 43
Fasting triglycerides (mg/dL)	149 ± 66	193 ± 97	158 ± 68
HDL-cholesterol (mg/dL)	41 ± 8	38 ± 8	42 ± 10
LDL-cholesterol (mg/dL)	122 ± 29	117 ± 33	140 ± 37
Non–HDL-cholesterol (mg/dL)	152 ± 34	155 ± 35	172 ± 38
BIA fat mass (%)	39.2 ± 13.0	39.0 ± 10.8	—
BIA fat-free mass (%)	60.8 ± 13.0	61.0 ± 10.8	—

NOTE. All results are expressed as mean ± SD.

No significant differences among treatment groups except as indicated: *P = .02 among the 3 groups by ANOVA and P = .009 for difference between dropouts and the Pancreas Tonic group.

latter subject was unblinded at the time of hospitalization and was discovered to have been receiving placebo. No statistically significant differences were seen among the groups for any of the parameters listed in Table 2, except for systolic blood pressure being higher in the dropouts compared with the Pancreas Tonic group.

All subjects were instructed to maintain their pre-existing oral antidiabetes medication regimens at a constant dosage throughout the study. However, among the 36 completed subjects, 4 subjects deviated from these instructions without informing the investigators beforehand. Of these individuals, 3 subjects (1 receiving placebo and 2 receiving active treatment) reduced their dosage of prestudy antidiabetes medications during the double-blind treatment period and yet experienced an HbA_{1c} reduction ranging from 0.7% to 1.5%. It is therefore unlikely that the study's findings were altered by any bias introduced by medication changes in these 3 subjects. The remaining subject, receiving active treatment in the lower stratum of entry HbA_{1c} levels, was exposed to an unknown dose of rosiglitazone for the final month of double-blind treatment. This subject had a change of HbA_{1c} from 9.2% at randomization to 8.6% at study end. Since no significant overall change in HbA_{1c} was seen in stratum 1 (see below), this medication change did not falsely bias the study's findings to any significant degree.

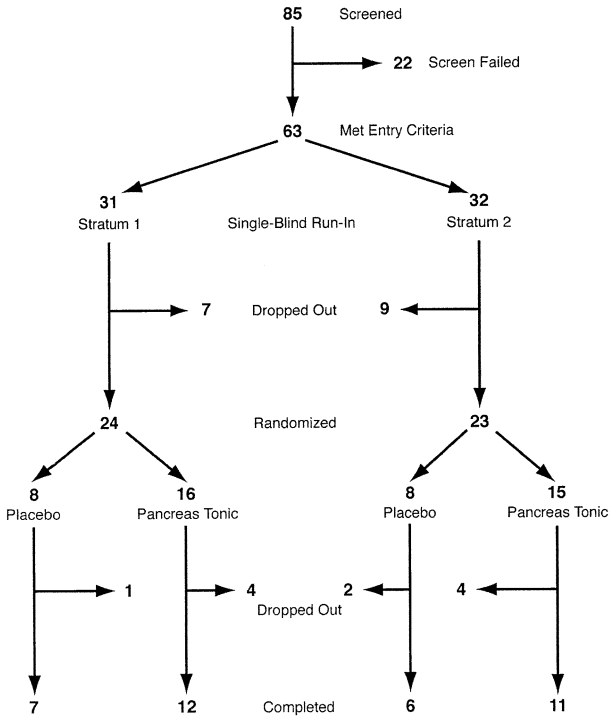

Fig 1. Subject enrollment and dropouts throughout the study. See text for explanations of dropouts.

Glycemic Control

Changes in HbA_{1c} levels for the 2 strata of HbA_{1c} levels at study entry are shown in Table 3 and Fig 2. A significant reduction of HbA_{1c} was seen with Pancreas Tonic treatment in the higher stratum subjects (entry HbA_{1c} 10.0% to 12.0%), while no significant changes were seen in the placebo group with the same HbA_{1c} level at study entry (Fig 2). The change

Table 3. HbA_{1c} Changes According to Treatment Assignment and Stratum

	Stratum 1		Stratum 2	
	Placebo	Pancreas Tonic	Placebo	Pancreas Tonic
Entry HbA_{1c} (%)	8.6 ± 0.8	8.8 ± 0.6	11.3 ± 1.1	10.9 ± 1.0
Randomization HbA_{1c} (%)	8.5 ± 1.3	9.4 ± 1.5	10.8 ± 1.4	10.1 ± 1.2
P (randomization v entry)	NS	NS	NS	.04
Final HbA_{1c} (%)	8.1 ± 1.4	9.5 ± 1.5	11.2 ± 1.8	8.8 ± 1.9
P (final v randomization)	NS	NS	NS	.004

NOTE. All results are expressed as mean ± SD. P values represent differences based on paired t tests.

Abbreviation: NS, not significant.

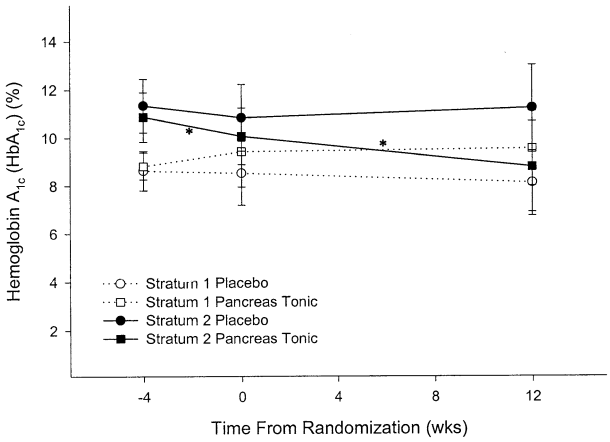

Fig 2. Changes in HbA_{1c} levels with Pancreas Tonic or matching placebo for subjects stratified according to entry HbA_{1c} level (stratum 1 placebo, ○; stratum 1 Pancreas Tonic, □; stratum 2 placebo, ●; stratum 2 Pancreas Tonic, ■). *$P < .05$ for the differences between randomization and study end and between entry and randomization in the stratum 2 Pancreas Tonic group.

in HbA_{1c} level between study entry and randomization was also statistically significant in the higher stratum Pancreas Tonic group. Although this may suggest that lifestyle changes instituted during the run-in phase may have added to the overall improvement in HbA_{1c} seen during the double-blind phase, Fig 2 shows an apparent divergence of the HbA_{1c} levels between the stratum 2 subjects receiving Pancreas Tonic and placebo in a double-blind fashion.

We also analyzed these changes in HbA_{1c} over time using ANOVA of repeated measures, accounting for the interacting effects of both treatment assignment (Pancreas Tonic *v* placebo) and stratum assignment (higher *v* lower). Changes in HbA_{1c} were not significant when either treatment or stratum was included in the model, but became significant when both factors were included together ($P = .036$). Thus, the change in HbA_{1c} seen in the stratum 2 Pancreas Tonic group was a function of both exposure to Pancreas Tonic and a higher baseline HbA_{1c} level.

There were no significant correlations between the known duration of diabetes and the change in HbA_{1c} response between randomization and study end for either stratum. FPG concentrations were also not significantly different in any of the treatment groups.

Other Secondary Outcome Variables

No differences in total cholesterol, fasting triglycerides, HDL-cholesterol, calculated LDL-cholesterol, non–HDL-cholesterol, systolic or diastolic blood pressures were seen throughout the treatment period; a nonsignificant difference in BMI noted at study entry persisted and remained statistically nonsignificant throughout the study. There were also no statistically significant changes in percent body fat and fat-free mass as a result of treatment with Pancreas Tonic.

Intravenous Glucose Tolerance Tests and Meal Challenge Tests

There were no significant changes in any group for the minimal model indices of S_i, S_g, AIR_g, or the DI. In the meal challenge tests, a significant ($P = .02$) decrease in glucose AUC was seen in the stratum 1 placebo group, and a significant ($P = .03$) decrease in insulin AUC was seen in the stratum 1 Pancreas Tonic group; no significant changes were seen in the stratum 2 groups. Since we saw significant changes of HbA_{1c} only in the stratum 2 Pancreas Tonic group and not in either of the stratum 1 groups, these changes were not clinically important.

Adverse Events and Safety Parameters

The only statistically significant changes seen with Pancreas Tonic treatment were slight decreases in hemoglobin (13.4 ± 1.7 g/dL at randomization; 13.0 ± 1.6 g/dL at study end; $P = .04$) and platelet count ($259 \pm 66 \times 10^3/\mu L$ at randomization; $246 \pm 73 \times 10^3/\mu L$ at study end; $P = .04$) that remained within their respective normal ranges. No significant changes were seen in other hematologic parameters (hematocrit and leukocyte counts), general chemistry (electrolytes, urea, creatinine, calcium), hepatic transaminases and liver function tests (aspartate and alanine aminotransferases, alkaline phosphatase, bilirubin, albumin), and routine urinalyses (urine protein, blood and leukocytes) between randomization and study end with Pancreas Tonic. EKGs at randomization and study end did not reveal any statistically significant changes in P-R intervals, corrected QT interval time, S-T segments, or T-waves in the Pancreas Tonic group.

Nonspecific adverse events were noted infrequently through the study. In the placebo group, 5 subjects reported a total of 7 adverse events during the double-blind treatment period (nightmares, dizzy spells, abdominal pain, flank pain, insomnia, leg numbness, weakness on exertion), all of which resolved or improved during the study, as well as 2 adverse events during the placebo run-in period (headache, ear pain). In the active treatment group, 6 subjects reported a total of 5 adverse events during the double-blind treatment period. This included sore throat, itchy eyes, and migraine headache, which resolved spontaneously; 1 subject had an exacerbation of back and leg pain, which persisted through the study; 1 subject reported mild hypoglycemia that was attributed to an inconsistent eating pattern and resolved with lifestyle modifications. The active treatment group also reported 2 adverse events during the placebo run-in phase (gastrointestinal side effects attributed to metformin use and flushing sensation in the face). No other hypoglycemic events were noted in any of the subjects. In general, Pancreas Tonic was well tolerated by all subjects receiving active treatment.

Quality of Life Indices

Results of a modified SF-36 quality-of-life index were obtained from study subjects. Paired responses (at randomization and end-of-study) were available for 20 subjects. Results show no significant changes in treatment satisfaction indices pertaining to symptomatology, general feelings, or perceived health status in either treatment group.

DISCUSSION

We have shown, in a randomized, double-blind, placebo-controlled study that therapy with Pancreas Tonic 3 times a day for 3 months significantly lowers HbA_{1c} levels in those type 2 diabetic subjects entering the study with a baseline HbA_{1c} level between 10.0% to 12.0%. We believe that this is the first objective study demonstrating the intermediate-term glucose-lowering efficacy of an Ayurvedic herbal therapy for type 2 diabetes mellitus.

A true glucose-lowering effect of various components of Pancreas Tonic is supported by both preclinical and clinical evidence.[8,9] Pterocarpus marsupium (*P marsupium*, also known as false teak) is a large deciduous tree found in central India. In a short, uncontrolled study of extracts of the bark of *P. marsupium* in patients with type 2 diabetes, fasting and postprandial glucose levels, as well as HbA_{1c}, were lowered significantly, without an increase in hypoglycemic reactions.[10] Momordica charantia (*M charantia*, otherwise known as bitter melon) is a climbing vine commonly grown in Asia, Africa, and South and Central America. Various compounds have been isolated from its fruit, seeds, and seedlings and shown to have antidiabetic properties.[11] In human studies, the fruit juice of *M. charantia* improved glucose tolerance in an uncontrolled study in subjects with maturity-onset diabetes of youth (MODY).[12] Gymnema sylvestre (*G sylvestre*) is a woody, climbing vine found in central and southern India. Water-based extracts of its leaves yield a series of gymnemic acids that possess antidiabetic properties. In humans, an uncontrolled study in type 1 diabetic patients showed that the aqueous GS4 extract of *G sylvestre* transiently improved glucose control and lowered insulin requirements[13]; analogous findings were seen in an uncontrolled study of type 2 diabetic patients on oral agents.[14] Trigonella foenum graecum (also known as fenugreek) is a commonly cultivated annual herb that possesses a characteristic odor. An alkaloid known as trigonelline can be isolated from the seeds, and it appears to possess hypoglycemic properties.[8,15,16] In an unblinded study of type 1 diabetic patients, fenugreek significantly reduced fasting glucose, glucose tolerance, and serum lipids.[17] Also, in a randomized, double-blind, placebo-controlled 2-month study in type 2 diabetic patients, fenugreek seed extracts improved homeostasis model assessment (HOMA) insulin sensitivity, as well as insulin and glucose excursions during oral glucose tolerance testing, although changes in fasting glucose levels after 2 months were not different from placebo.[18]

In the present study, we found that a significantly lower HbA_{1c} level with Pancreas Tonic was confined to those subjects entering the study with a high HbA_{1c} level (10.0% to 12.0%). The reason behind this may relate to the magnitude of effect provided by Pancreas Tonic. It is well recognized that the absolute reduction of HbA_{1c} is more pronounced for individuals who have higher levels at baseline; this effect may be seen with any form of therapy in diabetes.[22,23] The possibility that Pancreas Tonic improved glucose control only in our stratum 2 subjects simply because of their higher baseline HbA_{1c} level needs to be tested with studies directly comparing Pancreas Tonic with existing pharmacologic agents. It may also be possible that the dose of Pancreas Tonic used in our study does not reflect its maximal efficacy, since no dose-response studies of Pancreas Tonic have been performed. However, since a significant difference was seen in the higher stratum within a randomized, double-blind, placebo-controlled study design, we believe that this represents a true physiologic effect of Pancreas Tonic for improving glucose control in type 2 diabetic patients who are poorly controlled.

Our observation of a significant change in HbA_{1c} levels between study entry and randomization in the stratum 2 Pancreas Tonic group points to significant improvements from dietary and lifestyle interventions alone. It may be argued that the HbA_{1c} decrease during the double-blind phase is merely a continuation of these lifestyle improvements. The benefits on glycemic control due solely to enrollment in a clinical trial may explain this discrepancy between the 2 strata of subjects, with the higher stratum subjects deriving greater benefit from improvements in lifestyle habits. During the run-in phase, subjects were blinded to the fact that they were receiving placebo, and although the stratum 2 placebo subjects also improved their HbA_{1c} levels by 0.5% during the run-in phase, a clear divergence occurred between the stratum 2 treatment groups through the double-blind phase. The effect of improved lifestyle therapy over time does not explain the apparent divergence in HbA_{1c} levels shown in Fig 2 between the Pancreas Tonic and placebo subjects within the same stratum.

We excluded from our analyses 27 individuals who failed to complete the study, including 11 who were randomized to double-blind medication before being excluded. The distribution of these 11 individuals among the treatment groups was consistent with the overall allocation and randomization ratios (5 and 6 allocated to stratum 1 and 2, respectively, and 3 and 8 randomized to placebo and Pancreas Tonic, respectively), so their exclusion should not have influenced the observed results. In terms of noncompliance with the study medication as a reason for exclusion, which may be another source of potential bias, the distribution was also consistent, with 1 of 3 receiving placebo and 4 of 8 receiving Pancreas Tonic excluded for reasons of definite or possible noncompliance with either the study medication or attending follow-up visits. Thus, it is not likely that any differential exclusion of these subjects between treatment groups biased our results.

Despite a significant change in HbA_{1c} in the higher stratum group, we failed to demonstrate any corresponding changes in the indices from the Minimal Model. We expected that reductions in HbA_{1c} would have been explained by significant changes in either S_i or AIR_g. It is possible that the FSIVGTT has insufficient sensitivity to detect subtle changes of insulin sensitivity in severely insulin-resistant patients, such as those with type 2 diabetes in our study. Indeed, the entity of $S_i = 0$ commonly seen in studies of type 2 diabetic patients using the Minimal Model approach has been a recognized limitation of this measure.[24] Steil et al[25] have previously reported the interday coefficient of variation of S_i in nondiabetic subjects to be 20.2% $\pm$ 3.2%, and according to our own power analysis based on our diabetic subjects, over 100 subjects per treatment arm would be required to demonstrate a moderate 30% change in S_i at 80% power. Fifteen of our 35 subjects completing both FSIVGTT procedures had $S_i = 0$ at either randomization or

end-of-study, consistent with the findings of the diabetic cohort studied by Saad et al.[24] Within stratum 2, 6 of 10 Pancreas Tonic subjects, compared to only 2 of 6 placebo subjects, had at least one $S_i = 0$, potentially resulting in a false-negative finding of a significant change of S_i in the Pancreas Tonic subjects. These statistics reflect the limitations of S_i by FSIVGTT for poorly controlled diabetic subjects like those included in our study. As for AIR_g, we would not have expected it to change significantly since first phase insulin response is already severely impaired in patients with type 2 diabetes.[26]

We also did not demonstrate any changes in the glucose or insulin excursions following the meal challenge that were congruent with the observed HbA_{1c} changes. However, the intra-individual variability of glucose responses to traditional oral glucose tolerance tests is known to be high.[27] It is possible that variable responses to a meal challenge also masked a subtle difference in glucose or insulin excursions.

We recognize that a significant decrease in HbA_{1c} unaccompanied by significant changes in other glycemic parameters is peculiar. In addition to the inherent limitations of the FSIVGTT and meal tolerance tests, it is possible that no significant changes in FPG were seen over time because Pancreas Tonic acts on postprandial rather than fasting glucose levels, although there is no evidence to support or refute this hypothesis. The double-blinded nature of this study and the divergence between treatment groups in stratum 2 in the absence of obvious biases introduced by subject exclusions all suggest a real treatment effect, while our ability to demonstrate corresponding improvements in secondary variables was possibly affected by their inherent insensitivity combined with the relatively small number of subjects in each treatment group. Further studies to clarify these questions of efficacy are necessary.

There were also no significant changes in traditional cardiovascular risk factors, such as blood pressure, BMI, body fat mass, lipid, and lipoprotein levels. Pancreas Tonic appears to be neutral with respect to these associated cardiovascular risk factors. Indeed, the overall safety of Pancreas Tonic for the 3-month period used in this study is clear, as shown by the excellent tolerability and lack of clinically significant adverse effects attributable to the drug. There were no clinically meaningful differences in the subjects' reporting of adverse symptoms or of any objective biochemical or hematologic parameters. The adverse events reported were sporadic and likely had no relationship to the study medication. Hypoglycemia did not appear to be a significant problem with the use of Pancreas Tonic in this study, although we cannot draw any general conclusions with respect to hypoglycemia in more well-controlled patients, because our subjects were out of control at study entry ($HbA_{1c} \geq 8.0\%$).

In summary, we have shown in a randomized, double-blind, placebo-controlled study that 3 months of treatment with Pancreas Tonic significantly improved HbA_{1c} levels in subjects with type 2 diabetes mellitus whose baseline HbA_{1c} levels were in the 10.0% to 12.0% range. In addition, no significant adverse events or laboratory changes suggesting adverse end-organ effects were noted within the scope of this study. The improvement in glycemic control may be weaker than that of established antidiabetes therapies in patients with similar baseline HbA_{1c} levels, although we cannot draw this conclusion without conducting proper comparison trials. There may also be inter-ethnic differences in therapeutic responses to Pancreas Tonic that remain undefined. In addition, we cannot draw any conclusions as to the mechanism of action of Pancreas Tonic, as our secondary outcome variables examining various aspects of glucose physiology did not show corresponding differences. The exact role that Pancreas Tonic should play in the therapeutic approach to the treatment of type 2 diabetes also remains to be established, including its efficacy in comparison to established antidiabetic agents, or its efficacy in combination with existing therapies. Nevertheless, we believe that this is the first study to report a significant effect on intermediate-term glycemic control by an Ayurvedic antidiabetic preparation using a prospective, randomized, double-blind, placebo-controlled design.

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