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Psyllium improves glycemic control in patients with type-2 diabetes mellitus

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ABSTRACT

Objective: This double-blind, placebo-controlled clinical study was designed to evaluate the effects of psyllium on fasting blood glucose (FBG) and HbA_{1c} in patients being treated for type-2 diabetes mellitus (T2DM).

Research design and methods: Patients were randomly assigned to 1 of the 3 treatment groups: placebo, psyllium 3.4 g BID or psyllium 6.8 g BID (just prior to breakfast and dinner). Patients had a total of 9 clinic visits during the 20-week study period (8 weeks baseline, 12 weeks treatment). A total of 37 patients [12 females, 34 Caucasians, mean age 62 years] were enrolled (8 in the placebo group, 15 in the psyllium 3.4 g BID group and 14 in the psyllium 6.8 g BID group) and were included in the Intent-to-Treat analysis.

Results: Both doses of psyllium significantly ($p<0.05$) lowered FBG compared to placebo at treatment weeks 4, 8, and 12. Psyllium 6.8 g BID significantly lowered HbA_{1c} compared to placebo at Week 8 (-0.58 ± 0.18, $p=0.003$), and both the 3.4 g dose and the 6.8 g dose of psyllium significantly ($p<0.05$) lowered HbA_{1c} compared to placebo at Week 12 (-0.53 ± 0.20, $p=0.013$; -0.65 ± 0.20, $p=0.003$, respectively).

Conclusions: The improvement in glycemic control observed with psyllium in T2DM patients was above that already conferred by a restricted diet (all patients) and a stable dose of a sulfonylurea (81.1% of patients). These data support that psyllium is an effective co-therapy for improving glycemic control in patients being treated for T2DM. NCT01582282.

1. Introduction

According to a 2011 report from the Centers for Disease Control (CDC), diabetes affects 26 million people of all ages (8.3% of the total U.S. population), and 11 million U.S. adults 65 years and older (26.9%) (Center for Disease Control and Prevention, 2011). In the same report, pre-diabetes represented an even larger percentage of the US population: 35% of U.S. adults ages 20 years; 50% of those aged 65 years or older (Center for Disease Control and Prevention, 2011). If the percentage for adults ages 20 years and older is applied to the entire U.S. population in 2010, it yields an estimated 79 million Americans with pre-diabetes (Center for Disease Control and Prevention, 2011). A 2010 estimate from the Centers for Disease Control (CDC) predicts that up to 1/3 of U.S. adults will have T2DM by 2050 (Center for Disease Control

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and Prevention). Diabetes is the leading cause of kidney failure, non-traumatic lower-limb amputations, new cases of blindness among adults in the U.S., a major cause of heart disease and stroke, and the seventh leading cause of death in the U.S. T2DM accounts for approximately 90–95% of all diagnosed cases of diabetes in adults (Center for Disease Control and Prevention, 2011). The Diabetes Prevention Program (DPP), a large prevention study of people at high risk for diabetes, showed that lifestyle interventions reduced the development of T2DM by 58% during a 3-year period (Diabetes Prevention Program Research Group, 2002). Research has found that lifestyle interventions are more cost-effective than medications in preventing or delaying the onset of T2DM in individuals with pre-diabetes (Center for Disease Control and Prevention, 2011). One lifestyle intervention to reduce the risks associated with T2DM is increasing consumption of fiber in the diet, but not all dietary fibers have a significant effect on glycemic control.

Dietary fibers that form a viscous gel when hydrated have been shown to have a variety of health benefits. Psyllium and β-glucan, both viscous soluble fibers, are clinically proven to lower serum cholesterol, leading to United States Food and Drug Administration (FDA) recognition for reducing the risk of cardiovascular disease. It has been established for over 3 decades that the viscosity of a dietary fiber is also highly correlated with improvement in glycemic control. In a study published in 1978, volunteers underwent 50-g glucose tolerance tests with and without the addition of several dietary fibers, including guar gum, a highly viscous (gel-forming) fiber (Jenkins et al., 1978). High viscosity native guar gum was effective for flattening the glucose response, but this effect was abolished when the guar gum was hydrolyzed (reduced viscosity). The study further showed that a reduction in mean peak rise in blood glucose was highly correlated with viscosity ($r=0.926$; $P<0.01$) and a delay in mouth-to-cecum transit time ($r=0.885$; $P<0.02$). The authors concluded that delayed nutrient absorption due to increasing the viscosity of chyme was an important property of a soluble viscous fiber in normalizing glycemic control (Jenkins et al., 1978). Since that time, numerous clinical studies have shown that a single dose of psyllium, a viscous soluble fiber, can lower postprandial peak glucose in healthy subjects, and that multi-week dosing of psyllium before meals can lower both FBG and HbA_{1c} in patients with Metabolic Syndrome and T2DM (Cicero, Derosa, Bove, Imola, Borghi, & Gaddi, 2010; Fagerberg, 1982; Frati Munari, Pinto, Andraca, & Casarrubitas, 1998; Karhunenetal.,2010; Pastors, Blaisdell, Balm, Asplin, & Pohl, 1991; Rodriguez-Morán, Guerrero-Romero, & Laczano-Burciaga, 1998; Sierra et al., 2001; Ziai et al., 2005). The purpose of the current study was to assess the dose–response effects of psyllium for improving glycemic control in patients with T2DM who are already being treated with a stable dose of an oral hypoglycemic drug and/or a restricted diet.

2. Methods

We conducted a two-site, double-blind, randomized, placebo-controlled, multi-dose clinical study consisting of two phases (an 8-week lead-in phase followed by a 12-week treatment phase), with targeted enrollment of 90 patients. The study was terminated early due to slow enrollment. Patients followed a restricted diet for all 20 weeks of the study. Dietary compliance was assessed by a study dietician using 3-day food diaries completed by the patients. Patients already taking a stable dose (≥3 months) of a sulfonylurea were maintained on that dose throughout baseline and treatment periods. The study included male and female patients, age 36–80 years, with a clinical diagnosis of T2DM (at least one year prior to the study) controlled by diet and/or an oral sulfonylurea, and an HbA_{1c} level between 6% and 10%. Patients were stratified into two strata: (1) diet alone, or (2) diet and oral hypoglycemic medication. Patients in each stratum were randomly assigned to 1 of 3 treatment groups: placebo, psyllium 3.4 g BID for a total of 6.8 g/day, or psyllium 6.8 g BID for a total of 13.6 g/day. For the 12 week treatment period, patients took psyllium (Metamucil®) or the fiber-free placebo BID, just prior to breakfast and dinner. In addition to the screening visit, patients visited the clinic 9 times during the 20-week period, fasting at least 12 h prior to each visit where a blood sample was drawn for analysis. Fasting blood glucose was assessed at dosing weeks 2, 4, 8, and 12. HbA_{1c} was assessed at dosing weeks 4, 8, and 12. Analysis of covariance was used to assess mean treatment difference from placebo at dosing time points. The model included terms for treatment and baseline laboratory value. The treatment effect was relatively consistent across investigative centers, i.e. no significant treatment-by-center interaction. Investigative center had no meaningful effect on results and was not included in the final model.

The in-life portion of this study was conducted in 1988, but due to early termination, the data did not undergo a per-protocol analysis. A recent search of internal databases for clinical studies on natural fiber supplements in individuals with pre-diabetes and patients with T2DM led to the rediscovery of these dose–response data. HbA_{1c} tests in this study were conducted using a Helena (Daiichi) HA-8110 analyzer prior to harmonization of standards and reference ranges for the assay. Raw test results have been recalculated as estimated DCCT equivalent HbA_{1c} values, permitting comparison of clinical outcomes to the reference range defined by the Steffes et al. (2005) landmark study. The following transform equation was derived from summary tables presented in Kullberg, Bergström, Dinesen, Larsson, Little, Goldstein, & Arnqvist (1996) paper which defined correlations between the standard DCCT test and several other HbA_{1c} methods which were used in preceding years (DCCT Equivalent = 1.0183 × (HA-8110) + 0.8286).

3. Results

Thirty-seven patients were enrolled, 30 of whom (81.1%) were taking a stable dose of a sulfonylurea [glipizide (5 patients) or glyburide (25 patients)] for glycemic control. Four patients (2 in each psyllium treatment group) withdrew from the study (1 patient in each psyllium group due to an adverse event, 1 patient was lost to follow-up, and 1 patient had a blood glucose level outside of the protocol required levels). The

statistical analysis was conducted on the Intent-to-Treat population (all 37 patients). Demographic and baseline characteristics (Table 1) were reasonably well-balanced except for FBG; the placebo, low-dose psyllium, and high-dose psyllium group means were 212.5 mg/dL, 201.7 mg/dL and 186.2 mg/dL, respectively. Both doses of psyllium significantly ($p<0.05$) lowered FBG compared to placebo at Weeks 4, 8, and 12 (Fig. 1 and Table 2). Pysllium 6.8 g BID significantly ($p<0.05$) lowered HbA_{1c} compared to placebo at Week 8, and both doses of psyllium significantly ($p<0.05$) lowered HbA_{1c} compared to placebo at Week 12 (Fig. 2 and Table 2). At Week 12, both the 3.4 g BID and 6.8 g BID psyllium doses lowered FBG versus placebo by 30.6 mg/dL and 40.7 mg/dL, on average, respectively. Mean treatment differences versus placebo with respect to HbA_{1c} at Week 12 were 0.53 and 0.65 for the 3.4 g BID and 6.8 g BID psyllium doses, respectively. Adverse events were non-serious in nature and distributed approximately equally across all three treatment groups (80–88% of patients for each treatment group). Two patients in the high dose psyllium group, both taking an oral sulfonylurea drug (glyburide and glypizide), reported transient symptoms consistent with episodes of hypoglycemia, but continued in the study.

4. Discussion

While it is generally recognized that dietary fiber is "good for you" (Slavin, 2008; Why is it important to eat vegetables, 2011), and there is general agreement that most people in the United States do not consume enough dietary fiber (Park et al., 2005; U.S. Food and Drug Administration, 2011), it may be less well known that a physical characteristic of fiber, specifically viscosity (gel-formation), drives efficacy in lowering cholesterol and improving glycemic control. Psyllium, a viscous soluble fiber, is clinically proven to significantly lower total- and LDL-cholesterol in patients with hypercholesterolemia (Agrawal, Tandon, & Sharma, 2007; Anderson, Floore, Bazel, O'Neil, & Balm, 1991; Anderson, Allgood, Turner, Oelgten, & Daggy, 1999; Bell, Hectorne, Reynolds, Balm, & Hunninghake, 1989; Everson, Daggy, McKinley, & Story, 1992; Garvin, Forman, Eiseman, & Phillips, 1965; Jayaram, Prasad, Sovani, Langade, & Mane, 2007; Jenkins et al., 1997; Levin, Miller, Muesing, Stoy, Balm, & LaRosa, 1990; Maciejko, Brazg, Shah, Patil, & Rubenfire, 1994; Moreyra, Wilson, & Koraym, 2005; Spence et al., 1995; Summerbell, Manley, Barnes, & Leeds, 1994; Weingand et al., 1997; Wolever et al., 1994a, 1994b). While the cholesterol lowering efficacy of psyllium is well studied and FDA-recognized (Food and Drug Regulations), it may be less well known that the same viscous nature of psyllium also decreases the rate of glucose absorption and carbohydrate degradation in the small bowel, attenuating peak postprandial serum glucose and insulin following a single dose, and improving glycemic control in pre-diabetes and T2DM with repeat dosing (Cicero et al., 2010; Fagerberg, 1982; Frati-Munari et al., 1998; Karhunen et al., 2010; Pastors et al., 1991; Rodriguez-Morán et al., 1998; Sierra et al., 2001; Ziai et al., 2005). Improvement in glycemic control by consuming dietary fiber has been shown to be highly correlated with the viscosity of gelling fibers (greater viscosity = greater efficacy), and the benefit is abolished if the fiber is rendered non-viscous (e.g. hydrolyzed guar gum) (Jenkins et al., 1978). Insoluble fiber (e.g. wheat bran) and non-viscous soluble fiber supplements (e.g. wheat dextrin, inulin) do not exhibit these viscosity-dependent health benefits.

The current study was the first placebo-controlled study to assess the dose–response effects of psyllium for improving glycemic control in patients already being treated for T2DM. The data show that psyllium, dosed BID before meals, significantly lowered FBG for both doses at weeks 4, 8, and 12, and significantly lowered HbA_{1c} at Week 8 for the high dose (psyllium 6.8 g BID) and at Week 12 for both psyllium doses, versus placebo. The improvement in glycemic control observed with psyllium was above that already conferred by a restricted diet (all patients) and a stable dose of sulfonylurea (81.1% of patients). At each post-baseline measure, FBG for the high dose group was lower than the low dose group (Fig. 1, NS). While further assessment of a dose–response is

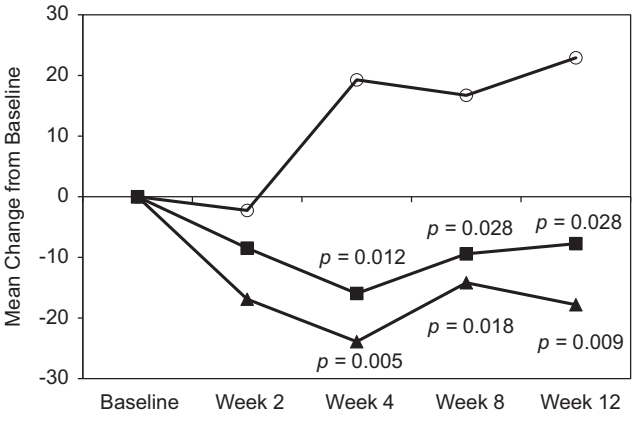

Fig. 1 – Fasting blood glucose (mg/dL) response to treatment. Both doses of psyllium significantly ($p<0.05$) lowered fasting blood glucose compared to placebo at weeks 4, 8, and 12 (placebo = circle; psyllium 3.4 g BID = square; psyllium 6.8 g BID = triangle).

Table 1 – Demographic and baseline values.

Parameter	Placebo BID (N = 8)	Psyllium 3.4 g BID (N = 15)	Psyllium 6.8 g BID (N = 14)
Male (%)	6 (75%)	10 (67%)	9 (64%)
Age (year) mean (SD)	56.5 (9.99)	61.8 (9.39)	64.8 (8.42)
Weight (lbs) mean (SD)	192.0 (38.27)	179.7 (21.25)	184.5 (36.94)
FBG (mg/dL) mean (SD)	212.5 (21.47)	201.7 (17.07)	186.2 (24.71)
HbA_{1c} (%) mean (SD)	7.6 (0.63)	7.4 (0.47)	7.6 (0.49)
Taking oral sulfonylurea (%)	6 (75%)	13 (87%)	11 (79%)

Table 2 – Efficacy results.

Parameter visit	Treatment	N	Change from baseline least squares mean (SE)	Treatment comparison p-value	
				Psyllium 3.4 g BID	Psyllium 6.8 g BID
Fasting blood glucose (mg/dL)					
2 Weeks	Placebo BID	8	−2.26 (10.52)	0.638	0.321
	Psyllium 3.4 g BID	13	−8.47 (7.90)		0.493
	Psyllium 6.8 g BID	11	−16.89 (9.03)		
4 Weeks	Placebo BID	8	19.28 (10.70)	0.012	0.005
	Psyllium 3.4 g BID	13	−15.96 (8.00)		0.508
	Psyllium 6.8 g BID	13	−23.91 (8.47)		
8 Weeks	Placebo BID	8	16.72 (9.23)	0.028	0.018
	Psyllium 3.4 g BID	13	−9.42 (6.90)		0.644
	Psyllium 6.8 g BID	13	−14.18 (7.31)		
12 Weeks	Placebo BID	8	22.91 (10.71)	0.028	0.009
	Psyllium 3.4 g BID	13	−7.73 (8.02)		0.411
	Psyllium 6.8 g BID	12	−17.81 (8.81)		
HbA_{1c} (%)					
4 Weeks	Placebo BID	8	0.06 (0.16)	0.312	0.317
	Psyllium 3.4 g BID	13	−0.15 (0.13)		0.982
	Psyllium 6.8 g BID	13	−0.14 (0.13)		
8 Weeks	Placebo BID	8	0.22 (0.14)	0.060	0.003
	Psyllium 3.4 g BID	13	−0.13 (0.11)		0.157
	Psyllium 6.8 g BID	13	−0.36 (0.11)		
12 Weeks	Placebo BID	8	0.26 (0.16)	0.013	0.003
	Psyllium 3.4 g BID	13	−0.27 (0.12)		0.498
	Psyllium 6.8 g BID	12	−0.39 (0.13)		

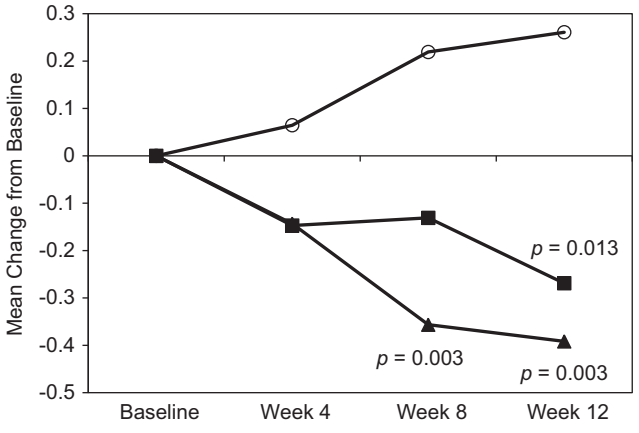

Fig. 2 – HbA_{1c} (%) response to treatment. Pysllium 6.8 g BID significantly ($p<0.05$) lowered HbA_{1c} compared to placebo at Week 8, and both doses of psyllium significantly ($p<0.05$) lowered HbA_{1c} compared to placebo at Week 12 (placebo = circle; psyllium 3.4 g BID = square; psyllium 6.8 g BID = triangle).

needed in a larger clinical study, these data support that supplementing a diet with psyllium, a viscous soluble fiber, is not an 'all or none' phenomenon, but can be individualized to meet a patient's specific needs.

These data are consistent with several published studies that assessed the effects of viscous soluble fiber for improved glycemic control in patients with pre-diabetes and T2DM (Cicero et al., 2010; Fagerberg, 1982; Frati-Munari et al., 1998; Karhunen et al., 2010; Pastors et al., 1991; Rodriguez-Morán et al., 1998; Sierra et al., 2001; Ziai et al., 2005). A recent 6-month, randomized, placebo-controlled study in 141 subjects with metabolic syndrome showed that both psyllium and guar gum, dosed BID with meals for 6 months, significantly improved objective clinical measures versus placebo, including FBG (psyllium. −28%; guar gum −11%), insulin (psyllium, −20%; guar gum −11%), BMI (psyllium, −7.2%; guar gum, −6.5%), HOMA index (psyllium, −39%; guar gum −17%), HbA_{1c} (psyllium, −10.4%; guar gum −10.3%), low density lipoprotein cholesterol (psyllium, −7.9%; guar gum −8.5%), and apolipoprotein B (psyllium, −11%; guar gum −6%) (Cicero et al., 2010). Psyllium, but not guar gum, also significantly lowered plasma triglyceride concentrations (−13.3%), and systolic (−3.9%) and diastolic (−2.6%) blood pressure (Cicero et al., 2010). At the end of the study period, 12.5% of patients in the psyllium group (2.1% of patients in the guar gum group) no longer met the criteria for the diagnosis of metabolic syndrome, while the prevalence in the placebo group did not change (Cicero et al., 2010).

For perspective, the multi-year intervention study conducted in people with pre-diabetes by the Diabetes Prevention Program Research Group showed that lifestyle intervention (diet and exercise) reduced the incidence of T2DM by 58% versus placebo, significantly ($p<0.05$) better than metformin, which reduced the incidence by 31% (Diabetes Prevention Program Research Group, 2002). These significant reductions in the incidence of T2DM with lifestyle interventions resulted from a mean change in FBG of approximately −5 mg/dL versus placebo at 6-months, and this difference was sustained over several years (Diabetes

Prevention Program Research Group, 2002). In the 6-month psyllium study in a Metabolic Syndrome population described above, supplementing with psyllium resulted in a −19.8 mg/dL decrease in FBG versus placebo at the end of 6 months (Cicero et al., 2010).

Studies in patients with T2DM show an even greater improvement in glycemic control with psyllium supplementation (Fagerberg, 1982; Frati-Munari et al., 1998; Karhunen et al., 2010; Pastors et al., 1991; Rodriguez-Morán et al., 1998; Sierra et al., 2001; Ziai et al., 2005). Ziai et al. (2005) assessed the effects of psyllium supplementation as an adjunct to a restricted diet and metformin therapy in a randomized, placebo-controlled study of 49 patients with T2DM. After 8 weeks of supplementation with psyllium 5.1 g BID, significant ($p<0.05$) reductions in FBG (mean change from baseline versus placebo, −89.7 mg/dL), and HbA_{1c} (mean change from baseline versus placebo, −3.0, $p<0.05$) were observed (Ziai et al., 2005). In another study of psyllium in T2DM, 125 patients (>90% taking a stable dose of a sulfonylurea, >7% taking insulin, >50% with vascular complications) were randomized to psyllium 5 g TID (or placebo) in combination with a low fat diet (Rodriguez-Morán et al., 1998). Psyllium treatment significantly reduced FBG levels at each assessment post-dosing (treatment weeks 2, 4 and 6), and showed an improvement of −35 mg/dL over placebo at 6 weeks ($p<0.01$), leading the authors to conclude that psyllium is a useful adjunct to dietary therapy in patients with T2DM (Rodriguez-Morán et al., 1998).

In conclusion, the results from the current dose–response study, taken together with published data, support that supplementing with psyllium before meals is an effective adjunct therapy to both dietary restrictions and hypoglycemic drugs for improving glycemic control in individuals with pre-diabetes and patients with T2DM. Given the significant improvement in glycemic control observed with psyllium, it is advisable to monitor blood glucose levels in patients already being treated for T2DM until a stable fiber regimen is achieved, as prescription medications may need to be adjusted. To facilitate long-term compliance with a new fiber regimen, it is advisable to introduce fiber therapy gradually, starting with one dose before a meal per day for the first week.

Author contributions

JM wrote the manuscript, RG and DR provided the statistical analysis of data, MF and RS contributed to the discussion and reviewed/edited the manuscript.

Dr. McRorie is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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