Psyllium

The Gel-Forming Nonfermented Isolated Fiber That Delivers Multiple Fiber-Related Health Benefits

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Psyllium is a natural, predominantly soluble isolated fiber that forms a gel when hydrated. The psyllium gel is not fermented and transits the entire gastrointestinal tract intact. In the small intestine, the psyllium gel increases chyme viscosity, which slows the degradation and absorption of nutrients, which significantly improves fasting blood glucose and hemoglobin A_{1c} levels in individuals with metabolic syndrome and type 2 diabetes mellitus (eg, −37 mg/dL). This delay in nutrient absorption prolongs satiety/delays hunger, leading to decreased energy intake and weight loss in overweight and obese patients. In the distal small intestine (terminal ileum), psyllium becomes more concentrated as water is absorbed, and the highly viscous gel interferes with the active reuptake of bile acids, which are captured in the gel and eliminated via stool. This decrease in the bile acid pool stimulates the liver to produce more bile. As cholesterol is a component of bile, the liver expresses low-density lipoprotein (LDL) cholesterol receptors to harvest LDL-cholesterol from the blood, thereby lowering both LDL-cholesterol (up to 24%) and total cholesterol (up to 20%) levels without affecting high-density lipoprotein cholesterol level. The cholesterol-lowering benefit of psyllium is also additive to the effects of statin drugs, with an effect equivalent to doubling the statin dose. In the large intestine, the nonfermented psyllium gel has a paradoxical "stool normalizing" effect: psyllium softens hard stool in constipation, firms loose/liquid stool in diarrhea, and normalizes stool form/reduces symptoms in irritable bowel syndrome. Psyllium is the only fiber recommended for treatment of constipation and irritable bowel syndrome by the American College of Gastroenterology. Taken together, psyllium is the only fiber supplement that provides 5 of the major health benefits identified by the Food and Drug Administration (cholesterol lowering, improved glycemic control, decreased energy intake/weight loss, decreased blood pressure secondary to weight loss, and laxation/regularity). Psyllium has also been shown clinically to be effective in disease states (eg, hypercholesterolemia, type 2 diabetes, obesity, chronic constipation, chronic diarrhea, hemorrhoids, ulcerative colitis, enteral nutrition–induced diarrhea, fecal incontinence, and irritable bowel syndrome). Taken together, the clinical data support the conclusion that "Fiber needs to gel to keep your patients well." Nutr Today. 2021;56(4):169–182

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In 2002, the Institute of Medicine published a definition of total fiber that differentiated "dietary fiber" (nondigestible carbohydrates and lignin that are intrinsic and intact in plants) from "functional fiber" (isolated, nondigestible carbohydrates that have been shown to have beneficial physiologic effects in humans).[1] By definition, fiber supplements (and fiber added to food) must show clinical evidence of a health benefit to be considered a "functional fiber." The Food and Drug Administration (FDA) initiated the Nutrition and Supplement Facts label rule (2016), which required marketers of fiber products to submit clinical evidence of a beneficial physiologic effect in order to be labeled as "fiber" on nutrition labels.[2] Based on the FDA's recommendations, 3 categories arise whereby isolated and synthetic fibers can be defined and classified for labeling purposes: (1) isolated fibers that already had an FDA-approved health claim (eg, psyllium and beta-glucan were approved under the Nutrition Labeling and Education Act to claim a reduced risk of coronary heart disease by lowering serum cholesterol levels); (2) isolated fibers (extracted from plant sources) that must submit clinical evidence of a beneficial physiologic effect; and (3) synthetic fibers that must submit clinical evidence of a beneficial physiologic effect. The FDA-approved beneficial physiologic effects included the following[3]:

1. Lowering cholesterol levels
2. Lowering blood glucose
3. Reduced energy intake
4. Lowering blood pressure
5. Improved laxation
6. Increased mineral absorption

The FDA required clinical evidence of only 1 of the above beneficial physiologic effects to be labeled as "fiber." As will be discussed in the following sections, psyllium has clinical evidence of efficacy in 5 of the above-listed beneficial physiologic effects. Psyllium is not fermented and therefore would not be expected to have, nor does it have an effect on mineral absorption. As will also be discussed in the following sections, psyllium provides additional beneficial physiologic effects that were not included in the FDA list (eg, effectively treats diarrhea and acts as a stool-normalizer in patients with irritable bowel syndrome [IBS]). As a point of clarification, this review focused specifically on the health benefits of psyllium. It was not intended to be a comprehensive review of other isolated fibers or dietary fiber.

What Is Psyllium?

Psyllium, also known as ispaghula, is the husk (outer coating) of the seed from the plant genus *Plantago*.[4] Because of specific climate requirements, the plant is primarily grown in India. Once harvested, the husk is mechanically separated from the seed by milling. Psyllium husk is predominantly a soluble fiber, composed primarily of arabinose and xylose and referred to as an "arabinoxylan."[4] Soluble fibers can be nonviscous (highly branched polymers that are randomly arranged) or viscous (long-chain linear polymers oriented parallel to adjacent fibers), and some viscous fibers are gel-forming (long-chain linear polymers oriented parallel to adjacent fibers and cross-linked).[5] Psyllium forms a cross-linked gel that holds/traps (T2DM) in its 3-dimensional structure. It is the high water-holding gel, which is not fermented and remains intact throughout the gastrointestinal tract, that drives all of the health benefits of psyllium.

HEALTH BENEFITS DERIVED FROM THE PHYSICAL EFFECTS OF PSYLLIUM IN THE SMALL INTESTINE

Psyllium Improves Long-term Glycemic Control in Metabolic Syndrome and Type 2 Diabetes Mellitus

Mechanism for Improved Glycemic Control

Psyllium forms a viscous gel that increases chyme viscosity, which slows the interactions of digestive enzymes with complex carbohydrates, thereby slowing the rate of digestion.[5] The increased viscosity also slows absorption of glucose and reduces peak postprandial blood glucose concentrations.[6] Normally, nutrients are absorbed early in the small intestine. This delay in nutrient absorption has the potential to deliver nutrients into the distal small intestine (distal ileum), where nutrients are not normally present. Nutrients in the distal ileum can stimulate mucosal receptors to initiate several metabolic responses, one of which is the release of glucagon-like peptide 1 into the blood stream. Glucagon-like peptide 1 is linked to several health effects, including decreased appetite and increased insulin secretion.[5] Considered together, the viscosity/gel-related mechanisms for improved glycemic control include lowering of the glycemic index of ingested foods and increasing the viscosity of chyme to slow glucose absorption and starch degradation in the small bowel, leading to a gel-dependent improvement in glycemic control for patients with T2DM and those at risk for developing the disease (eg, metabolic syndrome [Met Syn]). It is important to note that the mucosa of the small intestine has a surface area that is comparable with a tennis court, providing ample opportunity for nutrient absorption.[5] Although nutrient absorption is delayed with psyllium, nutrients are absorbed before reaching the large intestine.[5,7]

Psyllium and Cardiometabolic Risk Factors

Metabolic syndrome is a clustering of cardiometabolic risk factors that has been associated with greater risk of T2DM and cardiovascular disease (CVD).[8] With respect to isolated fibers, only gel-forming fibers, such as psyllium, have been clinically proven to significantly reduce the risk factors associated with Met Syn.[6]

A 6-month randomized, parallel study assessed the long-term effects of psyllium and guar gum supplementation in

141 patients with Met Syn.[9] All subjects were maintained on an American Heart Association Step 2 diet and were randomized to 1 of 3 treatment groups: restricted diet alone (control group), psyllium 3.5 g twice per day, or guar gum 3.5 g twice per day, both dosed 20 minutes before meals. After 6 months of treatment, both psyllium and guar gum showed a significant effect versus control ($P < .05$) on fasting plasma glucose (psyllium, −21.3% vs guar, gum −11.2%), insulin (−20.2% vs −10.8%, respectively), glycated hemoglobin (HbA_{1c}; −10.4% vs −10.3%, respectively), low-density lipoprotein (LDL) cholesterol (−6.9% vs −10.0%, respectively), apolipoprotein B (−10.5% vs −5.6%, respectively), and body mass index (BMI) (psyllium, −3.7% vs guar gum, −3.4%, respectively).[9]

Psyllium and Lowering Elevated Blood Glucose Levels in Patients With T2DM

More than 34 million Americans have diabetes (about 1/10), and most of these (90%-95%) have T2DM.[8] The percentage of adults with diabetes increases with age, reaching 26.8% among those 65 years or older.[10] T2DM most often develops in people older than 45 years, but more children, teenagers, and young adults are also developing it, most likely because of the increasing incidence of obesity. Unlike type 1 diabetes, an autoimmune disease in which the immune system attacks/destroys the insulin-producing beta cells of the pancreas, patients with T2DM still produce insulin. Over time, their body becomes resistant to insulin, and in response, the pancreas makes more insulin but eventually cannot keep up and blood glucose rises. A high blood glucose level is damaging to the body and can cause other serious health problems, such as heart disease, vision loss, and kidney disease.[11]

More than 4 decades ago, Dr David Jenkins established that the efficacy of fiber supplementation on attenuating peak postprandial blood glucose concentration is proportional to the viscosity of the fiber, and only gel-forming fibers have sufficient viscosity to provide a significant benefit.[12] Although acute studies yield data that are supportive of a benefit for gel-forming fibers on postprandial levels in T2DM,[6] long-term (multimonth) clinical studies are the standard to clinically prove a significant and sustained reduction in fasting blood glucose and hemoglobin A_{1c} levels. In a publication with 8 meta-analyses of 35 randomized controlled clinical studies that spanned 3 decades and 3 continents, psyllium (mean 10 g/d, taken in divided doses before meals) improved glycemic control proportional to the loss of glycemic control.[6] There was no significant effect on fasting blood glucose in healthy subjects with normal blood glucose control (euglycemia), a modest effect in pre-T2DM (up to −4.7 mg/dL), and a marked effect in patients being treated for T2DM (−37.0 mg/dL; $P < .001$).[6] Although the modest improvement in prediabetes (up to −4.7 mg/dL) may seem small, it is consistent with the glycemic benefit observed with long-term metformin therapy in the Diabetes Prevention Program.[13] After an average follow-up of 2.8 years, a similarly modest improvement in fasting blood glucose level (−4.6 mg/dL) was observed after metformin therapy in adults at high risk of developing T2DM. This reduction in fasting glucose led to a clinically meaningful reduction in the incidence of T2DM (−31%) in the metformin treatment group compared with the control group. Thus, 10 g/d psyllium improves glycemic control proportional to the loss of glycemic control and may help prevent or delay the onset of T2DM (Figure 1). The totality of clinical evidence shows that nonviscous soluble fibers (eg, inulin, wheat dextrin), viscous nongelling fiber (eg, methylcellulose), and insoluble fiber (eg, cellulose, wheat bran) have no effect on this gel-dependent improvement in glycemic control.[14]

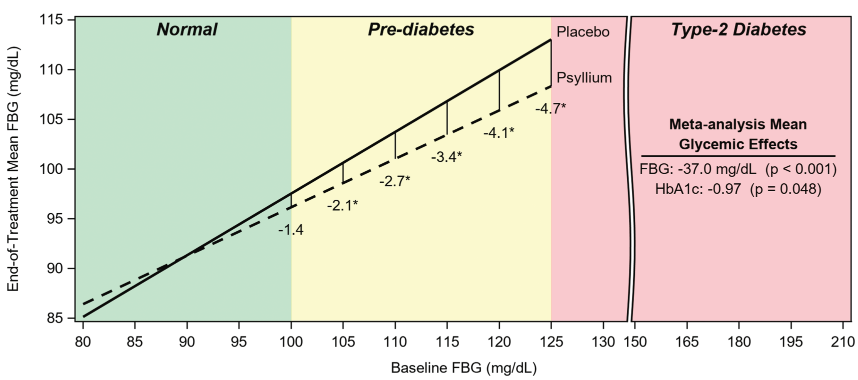

FIGURE 1. Psyllium fiber at 10 g/d improves glycemic control proportional to loss of glycemic control.[6] This figure depicts the results of meta-analyses[6] showing that psyllium at 10 g/d had no effect in normal (euglycemic) subjects, supporting a conclusion that psyllium will not cause hypoglycemia. Psyllium had a modest effect in prediabetes, and the greatest effect in patients being treated for T2DM. Although the effect in prediabetes (up to −4.7 mg/dL) may seem small, it is consistent with the glycemic benefit observed with long-term metformin therapy in the Diabetes Prevention Program,[13] where a similarly modest improvement in fasting blood glucose (−4.6 mg/dL) in persons at high risk of developing T2DM led to a clinically meaningful reduction in progression to T2DM (−31%). $^{*}P < .05$.

When added to standard treatments for T2DM, psyllium supplementation contributes to further improvement in blood glucose control in people being treated for T2DM. A randomized, placebo-controlled study assessed the effects of psyllium in 105 patients being treated for T2DM (92% taking a sulfonylurea, 8% taking insulin), more than 50% of whom were diagnosed with vascular disease.[15] Baseline data were collected for 6 weeks, followed by treatment data for 6 weeks with psyllium (5 g 3 times a day before meals) or placebo. Results showed that psyllium reduced fasting blood glucose level by 34 mg/dL (Figure 2),[15] comparable with the 37 mg/dL reduction found in the meta-analysis discussed above.[6] The authors noted that the higher dose (15 g/d) was well tolerated: "There was an excellent tolerance to Psyllium, without significant adverse effects)."[15] In summary, psyllium is an effective fiber therapy alone or in addition to medications for patients at risk for T2DM and patients being treated for T2DM. It is important to note that although psyllium has not been shown to cause hypoglycemia in patients with T2DM, psyllium may lower the requisite dose of the prescription medications that can cause hypoglycemia (eg, insulin, sulfonylurea). Patients being treated for T2DM should consult their prescribing healthcare provider and monitor their blood glucose when starting an effective fiber therapy.

Psyllium and Lowering Elevated Serum Cholesterol Levels

Coronary heart disease is the leading cause of death for men and women in the United States, with about 647 000 Americans dying of heart disease each year (1/4 deaths).[16] The Institute of Medicine established adequate intake guidelines for dietary fiber consumption based on a statistical association between a high-fiber diet and a reduced risk of heart disease.[1] The guidelines determined that consuming 14 g of dietary fiber per 1000 kcal of diet consumed was associated with this protective benefit. This translated to a recommendation for a dietary fiber intake of 38 g/d for adult men (ages 19-50) and 25 g/d for adult women (ages 19-50).[1] The adequate intake estimate decreased with age as calorie consumption decreased (>50 years: men, 30 g/d and women, 21 g/d). The average American diet falls far short of these recommendations, with only about 15 g/d dietary fiber consumed, leaving a significant "fiber gap."[1] It is a misconception, however, that all fibers can fill this "fiber gap" related to risk reduction for heart disease. Only gel-forming fibers are sufficiently viscous to lower elevated serum cholesterol levels, which can reduce the risk of coronary heart disease. Furthermore, only 2 gel-forming fibers, psyllium and beta-glucan, are FDA approved (via the Nutrition Labeling and Education Act) to claim a reduced risk for coronary heart disease by lowering serum cholesterol levels.[17]

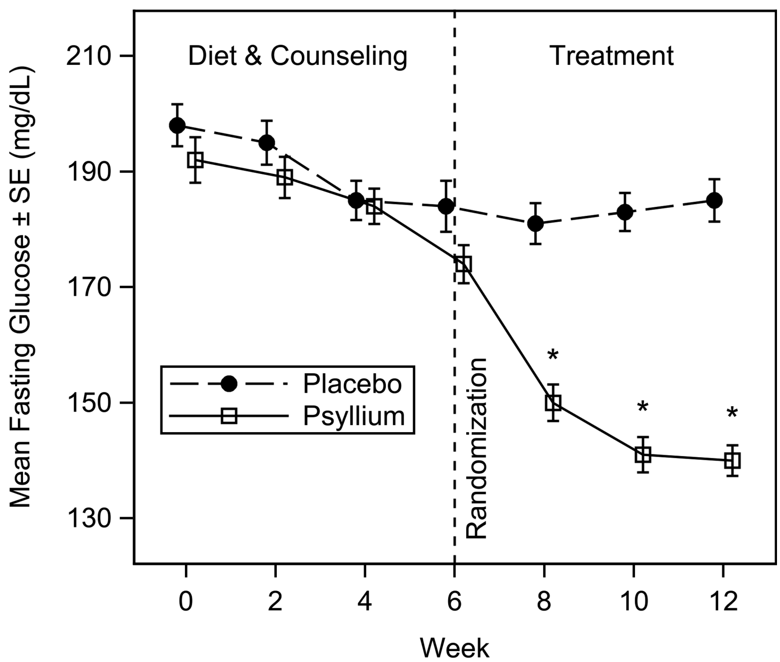

FIGURE 2. Psyllium provides a clinically meaningful reduction in fasting blood glucose in patients receiving drug treatment for T2DM.[15] This figure depicts the results of a randomized, placebo-controlled clinical study of the effects of psyllium (15 g/d) in 105 patients with T2DM (mean age, 57 years) being treated with a sulfonylurea (92%) or insulin (8%), and more than 50% were diagnosed with vascular disease. Baseline data showed that the restricted diet and counseling provided only a modest effect, whereas treatment with psyllium reduced fasting blood glucose an additional 34 mg/dL.[15] *$P < .05$.

Mechanism of Action for Psyllium and Cholesterol Lowering

The introduction of gel-forming psyllium into the small intestine lowers elevated serum cholesterol concentrations by trapping and eliminating bile acids. Bile, which is released into the duodenum in response to a meal, is highly conserved and normally recovered by active reuptake.[5,18] In contrast to nutrient absorption, which can occur along the entire length of the small intestine with a surface area approximately 250 m^2 (roughly the size of a tennis court), the active reuptake of bile acids occurs only in a short segment of the distal ileum. With water absorption along the length of the small intestine, psyllium becomes more concentrated in the distal ileum, forming a more viscous gel that traps and eliminates bile acids via stool. This reduction in the bile acid pool causes hepatocytes to compensate by stimulating LDL-receptor expression, which facilitates LDL-cholesterol clearance from the blood to synthesize more bile (cholesterol is a component of bile), thereby lowering serum LDL-cholesterol ("bad" cholesterol) and total cholesterol levels without affecting HDL-cholesterol level ("good" cholesterol).[5,18] Cholesterol lowering is a viscosity-dependent phenomenon, and only gel-forming fibers have sufficient viscosity to significantly lower cholesterol levels.[19] It is a myth that nonviscous fermentable fibers can lower cholesterol levels via fermentation byproducts. A review of the published literature yielded 17 randomized, well-controlled clinical studies that assessed the effects of soluble nonviscous, fermentable fibers (eg, prebiotics) on blood lipid concentrations, and none showed a significant difference in total or LDL cholesterol versus placebo.[14]

Psyllium Is Effective for Lowering Cholesterol Levels, Both Alone and in Combination With Statin Drugs

The effectiveness of psyllium for lowering elevated serum cholesterol concentrations was assessed in 21 randomized, well-controlled clinical studies (>1500 subjects) at doses of 6 to 15 g/d (most studies at 10 g/d).[14] All of the studies showed significant cholesterol-lowering effects, ranging from −6% to −24% for LDL cholesterol and −2% to −20% for total cholesterol, versus placebo.[14] The efficacy of psyllium was greatest in patients with high baseline cholesterol concentrations and in studies where the diet was not restricted. A recent randomized study assessed gel-forming psyllium 10.2 g/d (divided doses before meals) versus nonviscous wheat dextrin (10.5 g/d, used as a placebo in divided doses before meals) for 3 months in 20 free-living adults with hypercholesterolemia who were maintained on their usual diet.[20] The results showed that psyllium significantly ($P < .05$) lowered both LDL-cholesterol (−17%) and total cholesterol (−11%) levels without significantly affecting HDL-cholesterol or triglyceride levels, versus placebo (wheat dextrin) (Figure 3).[20]

A recent meta-analysis of 28 studies (n = 1924), with a median psyllium dose of 10.2 g/d for 8 weeks, confirmed the efficacy of psyllium for lowering elevated serum

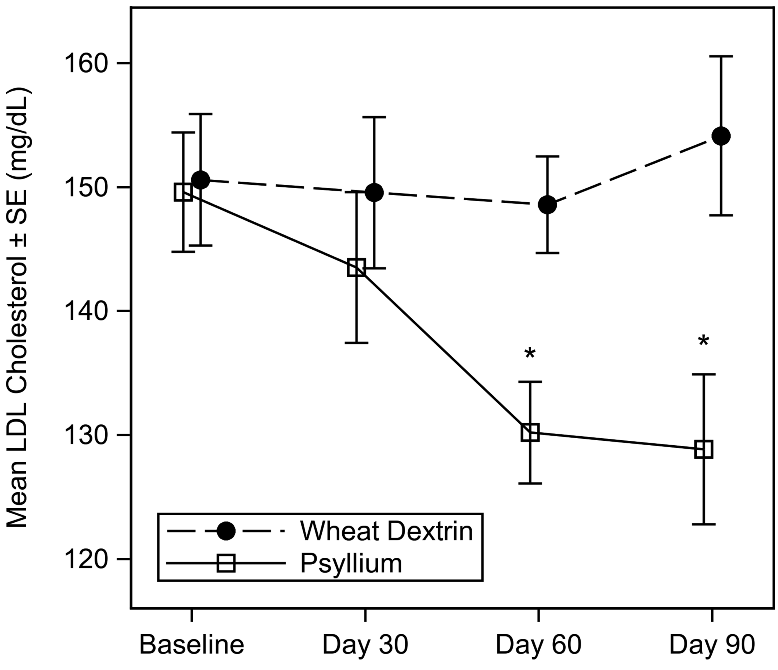

FIGURE 3. Gel-forming psyllium is superior to nonviscous wheat dextrin for lowering elevated serum cholesterol.[20] This figure depicts the results of a randomized study comparing the effects of gel-forming psyllium (10.2 g/d) to nonviscous wheat dextrin (10.5 g/d, placebo) for 3 months in free-living adults with hypercholesterolemia who were maintained on their usual diet. Results showed that psyllium significantly decreased LDL-cholesterol by 17% (and total cholesterol, 11%).[20] $*P < .05$.

LDL-cholesterol levels (−12.8 mg/dL) and other markers of CVD.[21] The authors concluded: "Psyllium fiber effectively improves conventional and alternative lipid markers, potentially delaying the process of atherosclerosis-associated CVD risk in those with or without hypercholesterolemia."[21] The cholesterol-lowering benefit of psyllium is also additive to the effects of statin drugs. A recent meta-analysis of 3 clinical studies (4–12 weeks in duration) showed that psyllium (mean, 10.8 g/d in divided doses before meals) provided a clinically and statistically significant ($P = .001$) cholesterol-lowering advantage for psyllium plus statin treatment over the same statin alone.[22] The authors concluded that adding psyllium to a statin regimen resulted in reductions in LDL-cholesterol levels equivalent to doubling the statin dose. This could be particularly important for patients who cannot tolerate higher doses of a statin drug.

In summary, psyllium is clinically proven to significantly lower LDL-cholesterol and total-cholesterol levels without affecting HDL-cholesterol levels. Psyllium is also FDA approved to claim a reduced risk of CVD by lowering elevated serum cholesterol levels.[17] An economic analysis found that if adults 45 years and older with elevated LDL-cholesterol levels (eg, ≥130 mg/dL) consumed psyllium 10.2 g/d, there could be an average savings of $870 million in healthcare costs and quality of life productivity gains (estimates from 2013-2020).[23]

Psyllium and Satiety/Hunger, Energy Intake, and Long-term Weight Loss/Management

There is a hierarchy of data associated with weight management. The lowest order of clinical evidence is the subjective assessment of satiety and hunger, which are short-lived feelings that may be predictive of energy intake at a subsequent meal. Energy intake is an objective measure of food (calorie) intake at a subsequent meal following a fiber dose and may be predictive of weight loss. It has been established that viscosity plays a key role in a fiber effect on satiety/hunger, energy intake, and weight loss.[24] As concluded in a review of fiber and satiety, "Increased viscosity delays gastric emptying and reduces the absorption of nutrients. The increased interaction with the cells that release satiety hormones stimulates the release of peptides involved in appetite regulation."[24]

Satiety/Hunger

Psyllium has been shown to be effective for increasing satiety and decreasing hunger in most, but not all, studies. Two clinical assessments of psyllium were reported in 1 publication.[25] The first randomized placebo-controlled study determined the effects of 3.4, 6.8, and 10.2 g of psyllium taken before breakfast and lunch for 3 days on satiety effects in 30 healthy adults. Results showed that all 3 psyllium doses resulted in directional and statistically significant mean reductions in hunger, desire to eat, and increased fullness between meals compared with placebo. Both higher doses were better than placebo or 3.4 g of psyllium.[25] The 6.8 g dose provided more consistent ($P = .013$) satiety benefits versus placebo and was selected as the dose for the second study. This second randomized placebo-controlled study determined the effects of psyllium 6.8 g (taken before breakfast and lunch on days 1 and 2 and before breakfast on day 3) on satiety in 44 participants receiving an energy restricted meal in the morning (breakfast) for 3 days. Results showed a significant ($P = .004$) decrease in the 3-day mean hunger and desire to eat scores, as well as an increase in fullness, for psyllium relative to placebo.[25]

Five additional studies assessed the effects of psyllium on satiety/hunger.[26–30] Two studies[26,27] assessed the satiety effects of 7.6 g of psyllium, and both showed a significant increase in satiety/decrease in hunger versus placebo ($P < .05$). One study[28] provided only 1.7 g of psyllium, which showed no significant effect on satiety. It is not clear why 2 higher dose studies showed either mixed results (22 g of psyllium)[29] or no effect on satiety (15 g of psyllium).[30] In summary, most clinical studies showed that 6.8 to 7.6 g of psyllium had a significant effect on satiety and hunger, which may be predictive of an effect on energy intake.

Energy Intake

Psyllium also reduces energy intake. In a double-blind randomized crossover study with 14 normal volunteers, psyllium (7.4 g) was assessed for its effect on gastric fullness, hunger, and energy intake.[26] Results showed that psyllium had no effect on gastric emptying, but hunger feelings and energy intake were significantly lower (13% and 17% lower, respectively; $P < .05$) following psyllium than during the placebo session. Furthermore, postprandial increases in serum glucose, triglycerides, and insulin levels were lower with psyllium than with placebo ($P < .05$). The authors concluded that "Psyllium reduces hunger feelings and energy intake in normal volunteers at reasonable dose and without requiring mixing with the meal. It does not act by slowing down the gastric emptying of hydro-soluble nutrients, but by increase in the time allowed for intestinal absorption, as suggested by the attenuating of the postprandial serum glucose, insulin and triglycerides curves."[26]

Weight Loss

Studies assessing weight loss should meet 4 criteria: (1) Subjects should be overweight/obese (normal-weight subjects do not show significant weight loss with added fiber), (2) studies should be of sufficient duration to exhibit significant weight loss (eg, 2-12 months), (3) fiber should be a sufficient dose and taken just before meals, and (4) included studies should not be a design that controls body weight as a confounding factor (eg, cholesterol-lowering studies are designed to maintain a stable weight). Psyllium has been shown to have a significant effect on weight loss in 8 well-controlled clinical studies. A 6-month clinical study assessed the long-term effects of psyllium and guar gum supplementation on 141 patients with Met Syn.[9] All subjects were maintained on an American Heart Association Step 2 diet and were randomized to psyllium or guar gum 3.5 g twice per day 20 minutes before meals. The control group was maintained on the restricted diet alone (no added fiber). Guar gum resulted in initial weight loss at 2 months, followed by slight weight regain at 4 and 6 months (Figure 4). In contrast, psyllium showed sustained weight loss at all time points (2, 4, and 6 months) (Figure 4). At the 6-month time point, psyllium provided sustained weight loss greater than that provided by a restricted diet alone.[9] Psyllium, guar gum, and diet alone all showed a significant reduction in waist circumference versus baseline (4.1, 5.2, and 2.5 cm, respectively). Both psyllium and guar gum also showed a significant ($P < .001$) reduction in waist circumference versus the restricted diet alone. Only psyllium provided a significant improvement in systolic (−4%) and diastolic (−3%) blood pressure at 6 months, presumably secondary to weight loss. A second randomized placebo-controlled study assessed the efficacy of psyllium (10 g/d in divided doses before meals) versus placebo for weight loss in 20 cardiology patients.[31] The 3-month study showed that psyllium significantly ($P < .05$) reduced body weight versus placebo and also showed a significant ($P < .05$) reduction in systolic (−3%) and diastolic (−5%) blood pressure. Note that in both studies, mean blood pressure was only in the prehypertension range (120–139/80–89), leaving room for only a modest improvement. Of the 2 weight loss studies that assessed blood pressure, both showed significant reductions that are presumably secondary to weight loss.

Other studies have confirmed the efficacy of psyllium for weight loss. A 3-month randomized controlled study in 77 constipated patients with type 2 diabetes dosed psyllium or flaxseed 10 g/d (divided doses) versus placebo, premixed in cookies, twice per day before meals.[32] Both the psyllium and flaxseed treatment groups showed significant weight loss ($P < .001$) versus the placebo group. A 3-month study randomized 72 obese subjects (mean BMI, 34.5 kg/m^2) to 1 of 4 treatment groups (n = 18 each): 2 groups remained on their usual diet, adding either placebo or psyllium 12 g 3 times per day before meals, and 2 additional groups were placed on a high-fiber healthy diet, adding placebo or psyllium 3.4 g, 3 times daily before meals.[33] Results showed that body weight, BMI, and percentage total body fat were significantly ($P < .05$) reduced in both psyllium treatment groups and the high-fiber healthy diet versus the regular diet placebo at 3 months. Reductions in all 3 measures were greater when psyllium was combined with the high-fiber diet ($P = .001$ for all 3 outcomes). A 10-week randomized placebo-controlled study in

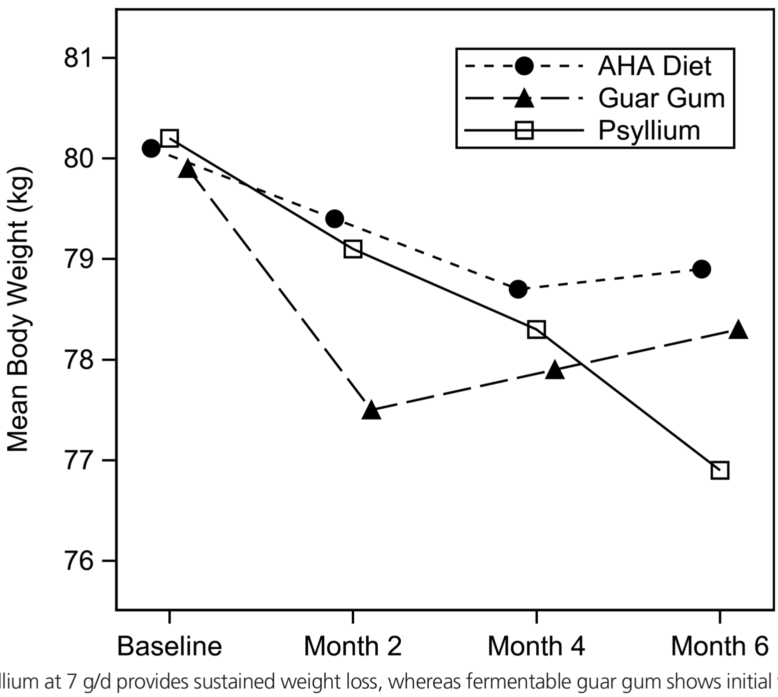

FIGURE 4. Nonfermented psyllium at 7 g/d provides sustained weight loss, whereas fermentable guar gum shows initial weight loss followed by weight regain.[9] This depicts the results of a randomized 6-month clinical study comparing the effects of an American Heart Association Step 2 diet alone or supplemented with psyllium or guar gum (both 3.5 g twice daily before meals) in 141 patients with Met Syn. The restricted diet alone and readily fermented guar gum showed weight loss followed by weight regain. In contrast, nonfermented psyllium showed sustained weight loss across all time points (2, 4, and 6 months).[9]

80 overweight/obese patients (mean age, 44.9 years) with nonalcoholic fatty liver disease consumed either psyllium or placebo (ground wheat) 10 g/d in divided doses before meals.[34] Both groups followed a weight loss diet and physical activity recommendations. Body weight was significantly (P = .03) reduced compared with placebo. A 3-month randomized placebo-controlled parallel design study assessed psyllium 10 g/d (divided doses before meals) versus placebo for weight loss in 51 patients with type 2 diabetes and chronic constipation.[35] Results showed that psyllium significantly (P < .001) reduced body weight by 2.0 kg versus placebo.

A 2-month randomized placebo-controlled parallel design study psyllium 10.5 g/d for weight loss in 40 overweight patients with type 2 diabetes.[36] Results showed that psyllium significantly reduced body weight by 3.7 kg versus placebo. A 12-month study in 159 overweight and obese adults compared the effects of a proprietary gel-forming product (PGX) to psyllium, both dosed at 5 g before meals (15 g/d), versus control.[37] The groups were not balanced at baseline (PGX group higher for BMI, body weight, and waist circumference), making any differences between treatments difficult to interpret. Psyllium showed significant (P < .01) reductions in body weight and BMI at 3 and 6 months and directional reductions at 12 months. Both fibers showed significant (P < .01) reductions in waist circumference (eg, −2 to −3 cm) versus control at 3, 6, and 12 months.[37] Taken together, 8 randomized placebo-controlled studies have shown that psyllium, when dosed just before meals for at least 2 months, provides significant weight loss in overweight/obese patients.

Two meta-analyses were recently published in online journals.[38,39] As discussed above, weight loss studies should assess overweight/obese subjects, for a sufficient duration, with a sufficient dose taken just before meals, and with a study design that does not maintain a consistent body weight. One of the meta-analyses included 23 publications and showed that psyllium had no significant effect on weight loss.[38] However, a critical review of the studies showed that more than half (12/23) could have been excluded from a weight loss meta-analysis. For example, 7 publications (30%) were cholesterol-lowering studies, which, by design, endeavor to maintain a constant weight throughout the study to minimize the risk of confounding (weight loss is a confounding factor for cholesterol lowering in a fiber study). Most (4/7) of the cholesterol-lowering studies specified that weight should be maintained throughout the duration of the study. Other studies included in the meta-analysis were too short in duration to evaluate weight loss (eg, only 2 weeks) or did not dose psyllium with meals, a requirement to facilitate satiety/weight loss. Removing the 12 studies would change the end result to favor weight loss for psyllium. The second meta-analysis[39] included 8 studies, but only 3 were included in the weight loss analysis, and the meta-analysis showed no significant effect for psyllium on weight loss. A review of all 3 studies, however, showed that each study resulted in a statistically significant weight loss for psyllium versus placebo. With all 3 studies showing significant weight loss, the meta-analysis should have also shown a significant reduction in weight loss for psyllium. The only rational conclusion is that the meta-analysis results are incorrect.[39] It is important to note that "publication" of a study should not be construed as synonymous with "scientifically rigorous" or "accurate," and all journals should not be afforded equal weight.

In summary, the totality of clinical evidence shows that psyllium was modestly effective for sustained weight loss when added to a usual diet and more effective when added to a high-fiber diet.

Psyllium Is Not Fermented in the Human Gastrointestinal Tract

For decades, psyllium has been characterized as "fermentable" based on in vitro fermentation data. It is important to note, however, that in vitro fermentation studies require that the bacteria-containing medium remain a very-low-viscosity liquid, which allows for continuous stirring for the duration of the test.[40] To accomplish this, psyllium is added to the medium at a very low concentration to prevent gel formation. This lack of gel formation allows bacterial access to fermentable fractions of psyllium that normally would be protected by the 3-dimensional structure of the gel (steric hindrance).[14,41] Under these in vitro conditions, methylcellulose (semisynthetic, chemically altered wood pulp) was rapidly fermented (up to 79% in 4 hours) whereas psyllium (natural fiber) was minimally fermented (up to 6% in 4 hours).[40] The small amount of gas produced in vitro was carbon dioxide, an odorless gas that is rapidly absorbed into the human blood stream and exhaled as breath gas without accumulating in the intestinal tract.[42] As shown in the following summary of clinical evidence, gel-forming psyllium is not fermented in the human gastrointestinal tract and does not produce "excess gas." The in vitro hypothesis[40] is not representative of the human experience and should be disregarded.

Six clinical studies assessed the fermentability of psyllium by both objective measures (eg, breath gas and rectal gas) and subjective measures (flatulence episodes). Two studies assessed the fermentability of psyllium in 8 healthy subjects using breath gas analysis, and both showed that psyllium was not fermented (Table 1).[43,44] A third study assessed objective measures of breath gas and rectal gas in 7 healthy subjects dosed psyllium 18 g/d for 15 days versus a negative control (Table 1).[42] Compared with the negative control, the high dose of psyllium showed directionally *lower* breath hydrogen output, significantly *lower* rectal gas

TABLE 1 6 Randomized Placebo-Controlled Clinical Studies Assessing the Fermentability (Gas Production) of Psyllium in the Gastrointestinal Tract

Study Reference	Increase in Breath Gases?	Increase in Rectal Gas Carbon Dioxide or Total Rectal Gas?	Increase in Flatulence Episodes?
Wolever and Robb, 1992[43]	No	–	–
Wolever et al, 1992[44]	No	–	No
Marteau et al, 1994[42]	No	No	No
Levitt et al, 1996[45]	No	–	No
Zumarraga et al, 1997[46]	–	–	No
Shulman et al, 2016[47]	No	–	–

hydrogen, and no difference in rectal gas carbon dioxide.[42] Recall that the in vitro data showed only a small increase in carbon dioxide (no change in the other gases measured).[40] As there was no increase in carbon dioxide in human rectal gas with a dose of psyllium that is almost twice the recommended daily dose,[42] the in vitro hypothesis was not representative of the human experience. Furthermore, this study showed that both fecal wet and dry weights significantly increased with psyllium versus control, demonstrating that psyllium survived transit and was present in the stool.[42] The finding that the psyllium gel was present in human stool was confirmed in another study where the gel was extracted intact from human stool after psyllium consumption.[48]

Two additional studies[45,46] assessed "excess gas" as the number of flatulence episodes per day, and both showed that psyllium did not increase flatulence (Table 1). The sixth randomized, placebo-controlled study assessed the effects of high-dose psyllium (12 g/d for 2 weeks) on flatulence episodes, abdominal pain, and microbiome changes in 103 children with IBS (Table 1).[47] The breath gas analysis showed that high-dose psyllium resulted in a directional *decrease* in both hydrogen and methane compared with control, consistent with results from 2 previously discussed studies.[39,40] There was also no significant change in the gut microbiome with psyllium, further supporting that psyllium is not fermented.[47]

Taken together, 6 randomized, placebo-controlled clinical studies directly assessed objective markers for fermentation/gas formation and subjective measures of "excess gas." All 6 studies showed that psyllium is not fermented in the human gastrointestinal tract/does not cause excess gas and the gel remains intact in stool. The in vitro hypothesis has been disproven and must be rejected. This is not a new concept. In 2007, the authors of a fiber review stated: "Psyllium is unique as a viscous fiber as it survives transit throughout the gut, while other viscous fibers are extensively fermented."[49]

Psyllium Has a Paradoxical "Stool Normalizing" Effect, Softening Hard Stool in Constipation, Firming Loose/Liquid Stool in Diarrhea, and Normalizing Stool Form in IBS

Constipation can be defined as infrequent elimination (eg, <3 bowel movements per week) of small/hard difficult-to-pass stools that require straining. Chronic idiopathic constipation is a common problem, and treatment guidelines recommend patients "increase fiber intake."[50] This generic recommendation presumes that all fibers, both dietary fiber and isolated fibers, are efficacious for constipation. This is a misconception that is not supported by clinical evidence.[14,51,52] A recent review identified 5 epidemiologic studies that explored an association between a high-fiber diet and a reduced risk of constipation, and only 1 of the 5 studies showed a statistical association.[51] It is important to note that although epidemiologic studies can assess for statistical associations between diet and disease incidence, they lack the control necessary to establish causation. The only way to establish causation is to assess isolated fibers in randomized well-controlled clinical studies. When so studied, fermentable fibers (eg, inulin, fructo-oligosaccharides, polydextrose) are not different from placebo for stool output or stool softening, debunking the myth that fermentable fibers may have a laxative effect by increasing the biomass.[14,52] This is not a new concept. In 2008, the "Position of the American Dietetic Association: Health Implications of Dietary Fiber" stated: "If the fiber is fully and rapidly fermented in the large bowel, as are most soluble fiber sources, there is no increase in stool weight."[53] It is also important to note that some fibers (eg, wheat dextrin, finely ground wheat bran) add only to the dry mass of stool, a stool-hardening effect that can be constipating.[14,51]

There are 2 known mechanisms by which a fiber can significantly increase stool water content and stool bulk, and both require that the fiber resist fermentation/arrive in stool intact, and increase stool water content: (1) poorly fermented coarse insoluble fiber particles (eg, coarse wheat bran) mechanically irritate the gut mucosa, stimulating water and mucous secretion; and (2) nonfermented gel-forming psyllium retains its water-holding capacity throughout the large bowel to resist dehydration/retain water.[51] Stool consistency is highly correlated with stool water content, and a small change in water content (eg, ±2%) has a marked effect on stool consistency: hard stool is 72% or less water; normal/formed stool, ≈74%; soft stool, ≈76%; loose stool, ≈80%; and liquid stool, more than 90%.[51,54] As stool is mostly water, significantly increasing stool water content increases stool output and softens hard stool, providing bulky/soft stools that are easier to pass.

A recent meta-analysis of 34 clinical studies showed that insoluble wheat bran had a modest effect on stool output increase in healthy subjects (2.9 g of stool per gram of fiber consumed, 2.9 g/g) but only a minimal stool output increase in constipated subjects (1.4 g/g).[51] These results suggest that the mechanism of action for coarse wheat bran, mechanical irritation of the gut wall, is less effective for overcoming the dehydrating effects of the large intestine when transit is slow in constipation. It is important to note that the data from healthy subjects were not predictive of efficacy in a constipated population for wheat bran, and the same may be true for other fibers.

As discussed above, finely ground wheat bran has a stool-hardening effect that can be constipating, and wheat bran nutrition labels do not provide information on whether the product is coarse or finely ground.[45] If treatment of constipation is the goal, then it is important to look for clinical efficacy of the fiber in a constipated population. The same meta-analysis described above also assessed 18 clinical studies on the efficacy of psyllium.[51] Analyses showed that gel-forming psyllium increased stool output by 4.8 g/g in a constipated population (3.4 times more effective than wheat bran) and a comparable increase, 5.0 g/g, in healthy subjects.[51] As discussed above, psyllium forms a 3-dimensional gel that is not fermented and remains intact throughout the gastrointestinal tract. The gel traps water/resists dehydration, retaining a higher water content than placebo throughout the large bowel.[55] For decades, wheat bran was incorrectly characterized as the "gold standard fiber for regularity."[56] The meta-analyses of 52 published clinical studies showed that psyllium is 3.4 times more effective than wheat bran in a constipated population, making psyllium the "gold standard fiber for regularity."[51]

Psyllium has also been shown to be more effective than docusate sodium (marketed as an over-the-counter [OTC] stool softener) for softening hard stools.[54] In a randomized study of 170 patients with chronic idiopathic constipation and hard stools (mean stool water content 71% at baseline), psyllium (5.1 g bid) increased mean stool water content to 74% (normal/formed stool) by dosing day 3, and the effect was sustained throughout the 2-week treatment period (week 2: mean 74%) (Figure 5). In contrast, stool water

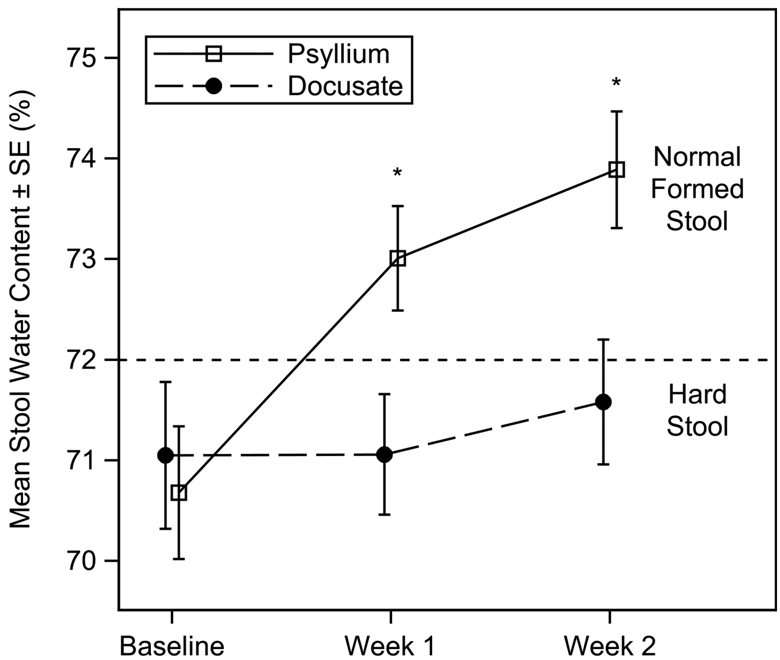

FIGURE 5. Psyllium at 10 g/d is more effective than docusate (Colace) for softening hard stool.[54] This figure depicts the results of a randomized clinical study comparing the effects of psyllium (5.1 g bid) and docusate (100 mg bid, marketed as a stool softener) in 170 patients with chronic idiopathic constipation and hard stools (mean stool water content 71%). Psyllium increased stool water content to 74% (normal/formed stool) by dosing day 3 and the effect was sustained throughout the 2-week treatment period (week 2: mean, 74%). In contrast, stool water content in the docusate sodium (100 mg bid) treatment group remained less than 72% (hard stool) throughout the study.[54] *$P < .05$.

content in the docusate sodium (100 mg bid) treatment group remained below 72% (hard stool) throughout the study (Figure 5).[54]

Psyllium is the most effective fiber for treating constipation and is FDA approved as an OTC treatment for occasional constipation. Taken together, these data show that psyllium increases stool output and softens stool across the range of the general population: healthy subjects, those with occasional constipation, and patients with chronic constipation. Surprisingly, not all products marketed as OTC bulk laxatives have evidence of clinical efficacy from placebo-controlled studies in people suffering from constipation. The FDA established the OTC laxative monograph[57] as a mechanism to begin regulating products that were already being marketed to consumers without FDA approval (eg, bulk fiber laxatives). It is important to note that products already on the market were "grandfathered" into the monograph without a requirement for evidence of clinical efficacy in patients with constipation. A literature search failed to identify any randomized, placebo-controlled clinical studies in patients with constipation for methylcellulose or calcium polycarbophil. This supports the statement made by the American College of Gastroenterology Chronic Constipation Task Force[58]: "Psyllium (eg, Metamucil, Konsyl) increases stool frequency in patients with chronic constipation (Grade B recommendation). There are insufficient data to make a recommendation about the efficacy of calcium polycarbophil (eg, Perdiem Fiber Therapy, Fibercon), methylcellulose (eg, Citrucel), and bran in patients with chronic constipation (Grade B recommendation)."

Diarrhea can be characterized as frequent loose/liquid bowel movements (>3 per day). In what may appear to be a paradox, psyllium can normalize stool form in constipation and diarrhea. The high water-holding capacity of the psyllium gel traps excess water in diarrhea, yielding formed stools and normalizing bowel movement frequency. Four randomized crossover clinical studies have evaluated the efficacy of psyllium in treating acute and chronic diarrhea.[59–62] Two studies assessed the effects of psyllium on stool consistency in acute phenolphthalein-induced diarrhea (stimulant laxative). The first crossover study assessed 9 subjects randomized to each of 4 treatments: psyllium 18 g/d, polycarbophil 6 g/d, wheat bran 42 g/d, and placebo, all dosed for 4 days.[59] Results showed that psyllium was the only fiber that significantly improved stool consistency ($P < .001$), more than doubling stool viscosity (35 622centipoise, soft/formed stool) versus placebo (16 470centipoise, liquid stool). Of interest, stool water content (90.8%) was identical for both placebo and psyllium treatments, supporting a conclusion that psyllium trapped excess water within the gel, yielding a soft/formed stool. Calcium polycarbophil and wheat bran had no significant effect on diarrhea.[59] The second crossover study of phenolphthalein-induced diarrhea assessed 6 subjects randomized to each of 4 treatments: psyllium 9, 18, and 36 g/d and placebo for 3 days.[60] Results showed a dose-response increase in stool consistency, from placebo (semiliquid) to psyllium 36 g/d (soft/semiformed). Similar to the results of the previous study,[55] stool water content remained high even though stool consistency normalized, supporting a conclusion that the psyllium gel traps excess water in loose/liquid stools to provide more formed stools.[60]

A third randomized crossover study compared the efficacy of psyllium (10 g/d) and loperamide (antidiarrheal, maximum 16 mg/d) in 25 patients with chronic diarrhea.[61] Chronic diarrhea was defined as more than 3 loose stools per day for more than 14 days, representing about 4% of the Western population. Before treatment, the median number of loose stools was 7 per day. Both treatments decreased stool frequency by half, but psyllium had the greatest effect on decreasing urgency ($P < .01$ vs loperamide) and

TABLE 2

Health Benefits	Isolated Fiber (Branded Example)								
	Psyllium (Metamucil®)	Beta-Glucan (Quaker Oats®)	Methylcellulose (Citrucel®)	Calcium Polycarbophil (Fiber Con®)	Partially Hydrolyzed Guar Gum (Benefiber Healthy Balance®)	Polydextrose (Fiber Well®)	Inulin (Fiber Choice®)	Wheat Dextrin (Benefiber®)	Wheat Bran (All-Bran®)
Glycemic Control	X	X							
Cholesterol Lowering	X	X							
Satiety	X	X							
Weight Loss	X	X							
Laxative	X		+/-*	+/-*					X**
Anti-Diarrheal	X								
IBS	X								
Natural	X	X					X		X
Fermented		X			X	X	X	+/-***	
Physical Properties	Gel-Forming		Non Gel-Forming						Insoluble
	Viscous				Non-viscous				
	Soluble								

Summary table of clinically proven health benefits.[6,14,18,51] *Both methylcellulose and calcium polycarbophil were grandfathered into the laxative monograph without placebo-controlled clinical evidence of efficacy in a constipated population. **Only coarsely ground wheat bran has a modest laxative effect. Finely ground wheat bran adds only to the dry mass of stool, a stool-hardening effect that can be constipating. ***Wheat dextrin is partially fermented. The nonfermented portion adds to the dry mass of stool, a stool hardening effect that can be constipating.

increasing stool consistency ($P < .05$ vs loperamide).[61] The fourth randomized crossover study induced acute diarrhea with lactulose (osmotic laxative) in 8 subjects and assessed the effects of psyllium (10.5 g/d) on gastric emptying, small bowel transit, and large bowel transit.[62] Psyllium significantly slowed both gastric emptying and large bowel transit versus placebo ($P < .05$), without significantly affecting small bowel transit time. The authors concluded that "The well-recognized benefit of psyllium in IBS is partly due to its treatment of constipation, but psyllium also benefits those with diarrhea and pain."[62] The high water-holding capacity of the psyllium gel has also been shown to normalize stool form/improve bowel function for patients with hemorrhoids,[63–66] ulcerative colitis,[67] enteral nutrition-induced diarrhea,[68,69] and fecal incontinence.[70,71] Note that psyllium was compared with loperamide in one of the fecal incontinence studies.[61] Results showed that both loperamide and psyllium improved fecal incontinence, but loperamide was associated with more adverse effects, especially constipation.[61] Taken together, these studies support a conclusion that psyllium is effective for normalizing stool consistency in acute and chronic diarrhea, without the risk of constipation that can be caused by loperamide.

Irritable bowel syndrome is a common functional gastrointestinal disorder characterized by recurrent episodes of abdominal pain associated with an altered bowel habit (eg, constipation-predominant, diarrhea-predominant, mixed) not explained by any structural or biochemical changes in the gut.[72] The prevalence of IBS is approximately 10% to 20% of the adult population in Western countries.[72] Clinical evidence supports that psyllium can normalize stool form and reduce symptoms in patients with IBS.[72–76] In the largest study to date, 275 patients were randomized to 1 of 3 treatment groups: psyllium 10 g/d, wheat bran 10 g/d, or placebo for 12 weeks.[72] During the first month, a significantly ($P < .05$) greater proportion of patients receiving psyllium reported adequate symptom relief for at least 2 weeks compared with placebo. After 3 months of treatment, symptom severity in the psyllium group was reduced by 90 points compared with 49 points in the placebo group ($P = .03$). Of note, the dropout rate was highest in those assigned to the wheat bran treatment group because of exacerbation of IBS symptoms, most likely caused by the mechanical irritation of the gut mucosa by coarse wheat bran particles, as mentioned in the discussion on constipation.[51] A second randomized, placebo-controlled clinical study in 80 patients with IBS showed that psyllium (10 g/d) significantly ($P < .02$) improved bowel habit and transit time in patients with constipation ($P < .05$).[73] Psyllium also significantly improved overall well-being, as captured in daily diary cards. The authors concluded that psyllium "significantly improves overall well-being in patients with irritable bowel syndrome, and in those with constipation favorably affects bowel habit and transit time."[73]

The ROME Foundation working group convened to review the effects of fiber on functional gastrointestinal disorders, and in a corresponding published review, they concluded: "When fiber is recommended for functional bowel disease, use of a soluble supplement such as ispaghula/psyllium is best supported by the available evidence."[74] In 2014, a meta-analysis of fiber supplementation studies, conducted to inform the American College of Gastroenterology Monograph on IBS, summarized the effects of 4 fibers: psyllium, bran, linseeds (also known as flax seeds), and "unspecified fiber."[75] The findings of this meta-analysis showed that only gel-forming psyllium provided a statistically significant improvement in IBS symptoms ($P < .05$). Based on these findings and other research conducted in IBS patients, the 2018 American College of Gastroenterology Monograph on Management of Irritable Bowel Syndrome concluded: "We recommend psyllium, but not wheat bran, for overall symptom improvement in IBS patients. (Recommendation: strong; Quality of evidence: moderate)."[76] In summary, nonfermented gel-forming psyllium is the only isolated fiber that both softens hard stool in constipation and firms loose/liquid stool in diarrhea. This dichotomous "stool normalizing" effect treats the altered bowel habits characteristic to IBS and in doing so reduces the pain and discomfort that are also characteristic to IBS. Psyllium is the only fiber specifically recommended for treatment of IBS by the American College of Gastroenterology.[76]

Avoiding Gastrointestinal Symptoms May Improve Long-term Compliance With a Fiber Regimen

Introduction of an effective fiber therapy may result in gastrointestinal symptoms (eg, bloating, discomfort), which may affect long-term compliance with therapy.[5] For nonconstipated subjects, psyllium should be initiated gradually, starting with a single daily dose (3.4 g/d) for the first week, then increasing by 1 daily dose each subsequent week until the therapeutic goal is achieved (usually about 10.2 g/d). For constipated patients, any introduction of an effective fiber therapy can carry a risk of discomfort/cramping pain unless the hard stool is eliminated before initiation of psyllium.[5] A reasonable suggestion is to first clear the hard stool with an osmotic laxative (eg, polyethylene glycol).[18] The ensuing cramping pain and potential loose stools will be associated with the osmotic laxative, not the fiber supplement. Once the hard stool is cleared, gradually introduce psyllium as described above. This may improve long-term compliance.[5,18]

CONCLUSIONS

Psyllium is a unique natural gel-forming fiber that provides multiple health benefits. In the small intestine, the psyllium gel increases chyme viscosity to slow the degradation and absorption of nutrients which improves glycemic control in Met Syn and patients being treated for T2DM. Psyllium also provides a satiety/weight loss benefit in overweight/obese patients. By interfering with the active reuptake of bile acids, psyllium lowers elevated serum cholesterol and reduces the risk of CVD. When added to statin drug therapy, psyllium provides an LDL-cholesterol–lowering effect equivalent to doubling the dose of the statin drug. In the large intestine, the nonfermented psyllium gel arrives intact in stool, providing a stool-normalizing effect that softens hard stool in constipation, firms loose/liquid stool in diarrhea, and normalizes stool form in IBS. Psyllium is 3.4 times more effective than wheat bran in constipation, making psyllium the gold standard fiber for regularity (Table 2).

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