Introduction

Heart disease is the leading cause of death in the US and an important cause of mortality worldwide. Risk factors for heart disease include age, high blood pressure, smoking, diabetes mellitus, and high cholesterol levels. There has been an increasing interest in the use of dietary supplements that may provide adjunctive therapy to standard medications, in order to take advantage of cardioprotective effects such supplements may have. Fiber products have classically been known to promote bowel regularity and are commonly used in different gastrointestinal pathologies. However, recent studies have also shown that a diet high in fiber may have beneficial effects in decreasing cholesterol and post-prandial glucose levels.

Fiber products include a spectrum of soluble and insoluble products. Sources of fiber include wheat bran, oat bran, barley, other grains and cereals, guar gum, dried beans and peas, fruits such as oranges and apples, and vegetables such as carrots (1). Although current recommendations for dietary fiber intake in adults is 25-30 gm per day, common serving sizes of fruits, vegetables, and grains contain only 1-3 gm per serving (2).

Psyllium is another type of soluble fiber. Although you may never have heard of psyllium, it is commonly found in consumer products such as Metamucil, Fiberall, and Konsyl, as well as high fiber breakfast cereals (3). In fact the US imports and consumes about 8000 metric tons of psyllium every year (4). In addition to being part of fiber formulations, psyllium supplements can also be found in granule, powder, wafer, and capsule forms. And importantly, because psyllium contains an increased amount of soluble fiber gram for gram compared to sources such as oat bran, its use may help fulfill daily dietary fiber recommendations more easily (5). This paper reviews the findings of studies analyzing the potential cardiovascular benefits of dietary psyllium, specifically focusing on its effects on total and LDL cholesterol.

What is Psyllium?

Psyllium is a soluble fiber that is derived from the seeds of the plant Genus Plantago, with the husk being the outer coat of the seeds. It is also referred to as Isabgol or Isapagula husk. The species *P. psyllium* and *P. ovale* are commercially grown in India, Pakistan, and in countries in Europe and the former Soviet Union. Psyllium products are grown for their mucilage content. Mucilage describes the clear, colorless gelling agents derived from plants which are able to increase in volume upon absorbing water (4, 6).

Chemically, psyllium is a highly branched polysaccharide derived from xylose, arabinose, and galactose, along with trace amounts of glucose, rhamnose, and uronic acid. When taken as a dietary product, it is not absorbed in the small intestine and passes onto the large intestine. In the large intestine, it gets partially broken down by normal bacterial flora, absorbs excess water, and increases its volume by about 10 times by forming a mucilaginous gel, which causes bulking of the stool and normal stimulation for stool elimination (4, 7-10).

As a stool bulking agent and promoter of overall stool regularity, psyllium has commonly been used in many gastrointestinal states, including constipation, diarrhea, irritable bowel syndrome, and hemorrhoids (3, 6, 11-13).

Cardiovascular Effects of Psyllium

Interest in psyllium has been growing as a broad range of studies have investigated its cardiovascular effects in addition to its gastrointestinal uses. A review of recent clinical studies and meta-analyses shows that psyllium may have beneficial cardiovascular effects by modestly lowering total and LDL cholesterol levels, with variable effects on HDL cholesterol, triglyceride (TG), and VLDL levels.

In a study by Anderson (2000), a meta-analysis of 8 clinical studies was done, which included 384 and 272 mild to moderate hypercholesterolemic people receiving either 10.2 g/d psyllium or cellulose placebo, respectively, over a period of 8 weeks or more, along with a low-fat diet. They found that psyllium intake adjunctive to a low-fat diet lowered total serum cholesterol by 4% ($p<0.0001$) and LDL cholesterol by 7% ($p<0.0001$) (14, 15). In another meta-analysis of 12 studies, which included a total of 404 mild to moderate hypercholesterolemic people taking 3 g or less of psyllium per day, psyllium intake was found to lower total cholesterol and LDL by 5% and 9% respectively (16). The differences in the cholesterol modifying effects of psyllium between the two meta-analyses may have been due to differences in patient populations, study types, treatment periods, and use of adjunctive therapies, in the individual studies examined. Nevertheless, the total percentage of cholesterol reduction appears to be broadly similar between the two meta-analyses.

In a double-blind, randomized control study comparing 16.5 g/d Minolest (psyllium and guar gum) versus placebo over 3 months in 83 hypercholesterolemic patients, total cholesterol was lowered by 3.2% ($p<0.05$) and LDL cholesterol by 5.5% ($p<0.05$) (17). However, significant changes in BMI, TG, and BP levels were not seen. In another double-blind, randomized control study by Davidson et al. (1998), 286 people were randomized to take either 0 (control), 3.4, 6.8, or 10.2 g/d psyllium, over a long term period of 24 weeks. Psyllium intake of 10.2 g/d was found to lower LDL levels by 5.3% ($p<0.05$) compared to the control group, with an effect that persisted over the course of treatment (18). No significant differences in either TG or HDL levels were found.

In another double-blind, randomized control study by MacMahon et al. (1998), 340 mild to moderate hypercholesterolemic people were randomized to either psyllium and diet modification, or placebo and diet modification, over a 6 month period. The psyllium and diet modification treatment was found to reduce total cholesterol by 7.7-8.9% and LDL cholesterol by 10.6-13.2% (19). The increase in cholesterol reduction compared to the Davidson et al. study may have involved the addition of diet modification to the treatment period.

The baseline cholesterol statuses of patients may also affect the cholesterol modifying effects of psyllium. In contrast to the moderate cholesterol reduction found in hypercholesterolemic patients, in one randomized cross-over study in which 63 normocholesterolemic people were treated with 12.5 g/d psyllium over 8 weeks, no significant cholesterol reductions were found (20). However, there have not been a substantial number of studies in normocholesterolemic patients to more generally predict the effectiveness of psyllium intake in this population.

In summary, the majority of recent clinical studies reflect that psyllium appears to modestly lower total cholesterol levels by anywhere from 3-8% and LDL levels by about 5-13% in mild to moderately hypercholesterolemic patients, with the actual effects depending on the various factors involved in each study (also see literature review by Chan, 1995) (21). Similar results have been found for other fiber products (22, 23). These factors include the dose taken, the total treatment period, and the baseline cholesterol statuses of patients (20, 24). Importantly, the context of a low or high fat diet along with other dietary modifications can also impact how

psyllium intake affects the lipid profiles of patients. Other studies have also shown that age, gender, and the hormonal status of patients may affect the therapeutic effects of psyllium (25-28).

The modest cholesterol lowering effect of psyllium fiber supplementation as a single agent in the context of a low-fat diet may be of primary benefit to patients with mild hypercholesterolemia. However, it will be interesting to identify the effects of psyllium supplementation as adjunctive therapy to standard cholesterol reducing medications such as statins and bile acid sequestrants (21, 28, 29). Potentially synergistic effects with the addition of psyllium can benefit a much wider patient population. Depending on dosage, statins can themselves lower total cholesterol by 30-40% (21). It will also be interesting to identify the effects of psyllium on other cardiovascular risk factors such as diabetes mellitus. In preliminary studies of psyllium use in Type II diabetic patients, high dose psyllium was found to decrease serum cholesterol as well as serum glucose levels (either all-day or post-prandial measurements) (30-33).

Possible Mechanisms for Psyllium-mediated Cholesterol Reduction

Both human and animal studies have been utilized to identify mechanisms for psyllium mediated cholesterol reduction. One of the primary mechanisms is thought to involve the bile acid cycle. Stool examinations have shown that there is an increased amount of bile acid excretion after psyllium use (34-37). Increased bile acid excretion may help decrease fat absorption and also deplete the amount of circulating bile acids, which can stimulate an increase in bile acid synthesis in the liver, which utilizes cholesterol precursors (38, 39). Psyllium may also affect the levels of proteins involved in lipid metabolism, including LDL receptors, apoprotein receptors, and hepatic enzymes such as HMG Co-A reductase and hepatic acyl-CoA cholesterol acyltransferase (ACAT) (34, 35, 40-42). And as a mucilaginous gel that affects the transit time of stool, which in turn affects the rate of absorption of nutritive substances, psyllium may theoretically decrease the absorption of cholesterol itself. However, further studies will need to be completed to corroborate the involvement of these mechanisms in the cholesterol modifying effects of psyllium.

Side effects and Contraindications for Psyllium

The use of psyllium is contraindicated in patients with severe abdominal pain, infections, vomiting, difficulty swallowing, esophageal stricturing or obstruction, chronic bowel narrowing or obstruction, bowel surgery, and flareup of diseases such as IBD. The use of psyllium is also contraindicated in anyone with prior allergic reactions to its exposure. Patients are recommended to stop psyllium use and notify a physician if constipation remains after one week of psyllium use or if there is any rectal bleeding. No known drug interactions are known for psyllium use. However, since psyllium may affect the absorption of medications, it should not be taken at the same time as other oral medications. Use of psyllium with bile acid sequestrants should be discussed with a physician before use since both these products may affect the bile acid cycle. (43-45)

Psyllium may have gastrointestinal side effects such as intestinal bloating, diarrhea, nausea, and mild abdominal cramping. Initial use of a lower dose and gradual dosage increase may help decrease these side effects. Adequate water intake is recommended to prevent choking

or any possible esophageal damage. Importantly, additional studies investigating the effects of long-term psyllium use on the absorption of vitamins, minerals, and electrolytes will need to be completed to ensure that physiologically significant changes in the absorption of these components does not occur.

Summary

Reviewing the data of recent clinical studies, the FDA has recently approved the use of the following statement on psyllium products: *"3g to 12g of soluble fiber from psyllium seed husk when included as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease,"* (46, 47). Psyllium appears to modestly decrease total cholesterol and LDL levels depending on factors such as dosage and the baseline cholesterol status of patients. Although its efficacy as a single agent in the context of a low-fat diet may be limited to mild hypercholesterolemic states, it may be an effective adjunctive therapy to use with standard medications such as statins, in order to maximize lipid risk reduction in patients.

Factors such as the general safety of psyllium intake (44) and its increased soluble fiber ratio per serving compared to other fiber products, along with its gastrointestinal benefits, make psyllium an attractive candidate to be used as a dietary supplement as part of daily fiber recommendations. However, further studies examining the effects of high dose psyllium, its long-term safety profile, and its effects on other cardiovascular risk factors such as diabetes, will be needed. In addition, the most effective and tolerable dosage of psyllium in both hyper- and normocholesterolemic patients will need to be identified before its long-term use can be encouraged in the general population.

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