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Fiber Supplements and Clinically Meaningful Health Benefits

Identifying the Physiochemical Characteristics of Fiber that Drive Specific Physiologic Effects

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8.1 INTRODUCTION

While there is no globally-accepted definition of dietary fiber, the Institute of Medicine (IOM) developed the following set of working definitions for fiber in the food supply: "*Dietary fiber* consists of non-digestible carbohydrates and lignin that are intrinsic and intact in plants" [1]. *Functional fiber* consists of isolated, non-digestible carbohydrates that have beneficial physiological effects in humans. The isolated fibers found in the vast majority of dietary supplements would, therefore, be considered "functional fiber," with the prerequisite of clinical evidence supporting the latter part of the statement, "… that have beneficial physiological effects in humans." Consistent with these definitions, this chapter will focus on the health benefits of dietary fiber supplements, as evidenced by the physiologic effects observed in well-controlled clinical studies. Unlike prescription and over-the-counter medications, fiber supplements have no requirements for pre-market approval by the Food and Drug Administration (FDA), so it can be challenging to determine which fiber supplements have well-controlled clinical evidence to support specific health claims. It is, therefore, important to have a working knowledge of the physical characteristics of fiber that drive specific physiologic effects so as to accurately discern which products provide a clinically meaningful health benefit supported by published clinical data.

It is widely recognized that dietary fiber is "good for you," [2–7], and that fruits, vegetables, and whole grains can be a good source of dietary fiber [3,7,8], but it can be a challenge to consume a sufficient quantity of these dietary sources of fiber daily to meet USDA recommendations for fiber consumption. Most servings of fruits, vegetables, and whole grains contain only 1–3 g of dietary fiber [9]. A recent (2014) review of data from the National Health and Nutrition Examination Survey database showed that only 8% of adults and 3% of children (including adolescents) consumed at least 3 whole grain ounce equivalents per day (≥3 whole grain ounce equivalents per day considered high consumption) [8]. The IOM Adequate Intake guidelines recommend 14 g dietary fiber per 1000 kcal consumed, which is about 25 g/day for women and 38 g/day for men [1]. In contrast to this recommendation, the vast majority (90%) of the United States population does not consume enough dietary fiber [10]. The average American consumes only 15 g of dietary fiber per day [11] and, for those on a low carbohydrate diet, total fiber intake may be less than 10 g/day [12]. Epidemiologic studies show that dietary fiber is strongly associated with a reduced risk of heart attack, stroke, and cardiovascular disease [13,14]. Given the low success rate in achieving recommended levels of fiber intake by consumption of high fiber foods, it is reasonable to consider fiber supplements as a convenient and concentrated source of fiber, which can facilitate meeting that goal.

It is important to recognize that, when considering the health benefits of dietary fiber, there is a key distinction between "replacement" and "supplementation." If a substantial portion of a diet is *replaced* by healthier, high fiber dietary components, then both the total calories consumed and the glycemic index of the diet [15] would be reduced, leading to a conclusion in epidemiological studies that a wide variety of fiber sources (e.g., fruits, vegetables, whole grains) can provide a detectable health benefit. It remains unclear, however, how much of that benefit is directly attributable to the effects of the dietary fiber, versus the elimination of less healthy components of the diet, a reduced calorie intake, and increased consumption of healthy constituents other than fiber derived from fruits, vegetables, and whole grains. In contrast to *replacement*, which includes a variety of fiber sources, a fiber *supplement* is typically an isolated fiber source that is consumed in addition to an existing diet. It therefore becomes essential to appreciate the unique physiochemical characteristics of each fiber supplement, and how these characteristics are, or are not, associated with one or more clinically meaningful health benefits. While some fiber supplements have extensive, reproducible clinical evidence for clinically meaningful health benefits, other fiber supplements do not. The term "fiber supplement" implies a benefit to one's health when consumed on a regular (e.g., daily) basis, but not all fiber supplements have clinical data at physiologic doses to support a clinically meaningful health benefit.

There are numerous *in vitro* and pre-clinical (animal) studies in the literature that suggest a health benefit is *possible* in humans, but evidence for a clinically meaningful health benefit should only be derived from well-controlled clinical studies. Individual clinical studies will be discussed, but the term "clinically demonstrated" will be reserved for fiber supplements with two or more well-controlled clinical studies that provide reproducible evidence of a health benefit. Further, health benefits should be demonstrated at doses that can reasonably and comfortably be consumed on a daily basis to facilitate long-term compliance. A fiber supplement is intended to *supplement* the fiber in a diet, not replace the dietary fiber naturally found in fruits, vegetables, and whole grains, which have other beneficial constituents that may not be found in a fiber supplement. The "Nutrition Facts" panel on food products characterizes a product as an "excellent" source of dietary fiber if it contains 5 g of fiber per serving. If consumed 4-times per day, an excellent source of fiber would provide 20 g fiber per day, representing 71% of the recommended fiber intake for a given day (based on 28 g fiber/2000 kcal) [16]. Therefore, it is a reasonable expectation that a fiber supplement should be capable of demonstrating a clinically meaningful health benefit at a total dose of 20 g/day or less. A fiber supplement that requires a total daily dose of fiber in excess of 20 g to detect a physiologic effect will not be considered to have a clinically meaningful health benefit.

While solubility (soluble versus insoluble) is commonly used to characterize dietary fiber, clinical evidence supporting specific health benefits, such as cholesterol lowering, improved glycemic control, and improvement in constipation and diarrhea, has often been inconsistent based on this single characterization. This inconsistency in the literature may be due to an under-appreciation of the importance of additional characteristics of specific fiber types, including particle size of insoluble fiber, viscosity/gel-formation for soluble fiber, and how processing might have altered the final product versus the original raw fiber. When considering the health benefits of fiber supplements, it is important to understand the physical characteristics of the marketed product for each fiber supplement, and the resulting health benefits that each product can, or cannot, provide. Health benefits derived from fiber supplements are primarily a function of the fiber's physical effects in the small bowel (e.g., cholesterol lowering, improved glycemic control, satiety/weight loss) and in the large bowel (improved stool form and reduced symptoms in constipation, diarrhea, and irritable bowel syndrome (IBS)). There are three main characteristics of fiber supplements that drive clinical efficacy: solubility, viscosity/gel-formation, and degree/rate of fermentation. Solubility defines whether a fiber supplement will dissolve in water (soluble) or remain as discreet insoluble particles [17]. Most fibers are not exclusively soluble or insoluble, so for the purposes of this chapter, the predominant characteristic will be discussed (e.g., a fiber that is 70% soluble will be considered a soluble fiber). For soluble fibers, viscosity refers to the ability of some polysaccharides to "thicken" when hydrated, in a concentration dependent manner [17–20]. Gel-formation refers to the ability of a subset of soluble viscous fibers to form cross-links, resulting in a visco-elastic gel [17,20]. Fermentation refers to degree to which a dietary fiber, after resisting digestion in the small bowel, can be degraded by gut bacteria, producing byproducts such as short chain fatty acids and gas [5].

Based on solubility, viscosity, and fermentation, fiber supplements can be divided into four clinically meaningful categories:

1. Insoluble (e.g., wheat bran): does not dissolve in water (no water-holding capacity); is poorly fermented, and can exert a laxative effect by mechanical irritation/stimulation of gut mucosa *if* particles are sufficiently large and coarse, but does not gel to attenuate diarrhea and the mechanical irritation could make diarrhea symptoms worse; small smooth particles (e.g., wheat bran flour/bread) have no significant laxative effect; do not significantly affect chyme viscosity, so would not reduce cholesterol concentration or improve glycemic control at physiologic doses.
2. Soluble non-viscous (e.g., inulin, oligosaccharides, resistant starches, wheat dextrin): dissolves in water; does not cause a significant increase in viscosity; does not form a gel (no significant cholesterol lowering effect, no significant improvement in glycemic control at physiologic doses); is rapidly fermented [rapid gas formation, energy harvest (calorie uptake) from fermentation by-products]; no significant laxative effect at physiologic doses; does not form a gel to attenuate diarrhea.
3. Soluble viscous/gel-forming, readily fermented (e.g., β-glucan, guar gum): dissolves in water, forms a viscous gel; increased chyme viscosity may improve glycemic control and lower serum cholesterol (if processing has not attenuated gel-forming capacity); readily fermented [gas formation, energy harvest (calorie uptake) from fermentation by-products]; does not retain its gelled nature throughout the large bowel, so cannot act as a stool normalizer.
4. Soluble viscous/gel-forming, non-fermented (e.g., psyllium): dissolves in water; forms a viscous gel; increases chyme viscosity to improve glycemic control and lower serum cholesterol; not fermented [no gas production,

no appreciable calorie harvest from fermentation by-products (weight control)]; retains gelling capacity throughout the large bowel that provides a stool normalizing effect (softens hard stool in constipation, firms loose/liquid stool in diarrhea).

8.2 SOLUBILITY, VISCOSITY, AND GEL FORMATION

Fiber supplements from carbohydrates are polymers of sugar molecules (monomers) linked together by bonds that resist degradation by digestive enzymes in the upper gastrointestinal tract. Solubility refers to the ability of fiber supplements to dissolve in water. Fibers that readily dissolve in water are considered water soluble, whereas insoluble fibers may disperse, float, or sink in water, but do go into solution and have no water-holding capacity or appreciable impact on viscosity (e.g., wheat bran). Many soluble fibers also do not appreciably alter viscosity or form a gel when dissolved in water, and these soluble fibers are referred to as "non-viscous" (e.g., inulin, wheat dextrin) [17]. Some soluble fibers increase the viscosity of a solution without forming a gel (e.g., methylcellulose), while others have the added ability to exhibit gel formation (e.g., guar gum, β-glucan, psyllium) [17]. The degree of "thickening" depends on both the chemical composition and concentration of the polysaccharide [17]. The capacity to form a gel is dependent on the ability of adjacent fibers to form cross-links, creating a three-dimensional network that can entrap water and behave like a solid (visco-elastic gel).

Fiber supplements have unique characteristics based on the types of sugars that they are made of, and the way in which the polymer chains interact with one another (e.g., straight chain versus highly branched chain). A straight-chain or linear polymer consists of a long string of carbon–carbon bonds between sugar molecules (Figure 8.1). The longer the straight chain, the greater the effect the fiber can have on viscosity when hydrated (Figure 8.2). In contrast, polymers with multiple branches at irregular intervals along the polymer chain are called branched polymers

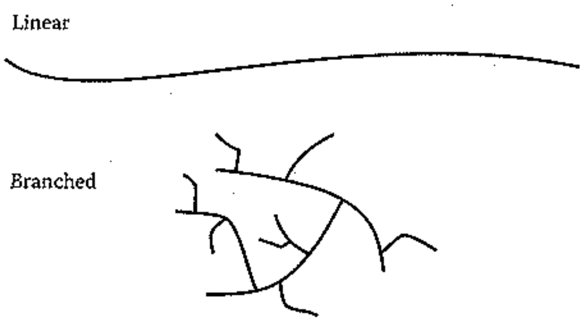

FIGURE 8.1 Linear versus branched polymers. This shows drawings representing linear and branched polysaccharides. Long-chain linear polymers (top) can have a similar molecular weight to highly branched polymers (bottom), but the relative effect on viscosity is much greater for linear polymers than for branched polymers. (From John D. Keller, Jr., Keller Konsulting LLC, Freehold, NJ. With permission.)

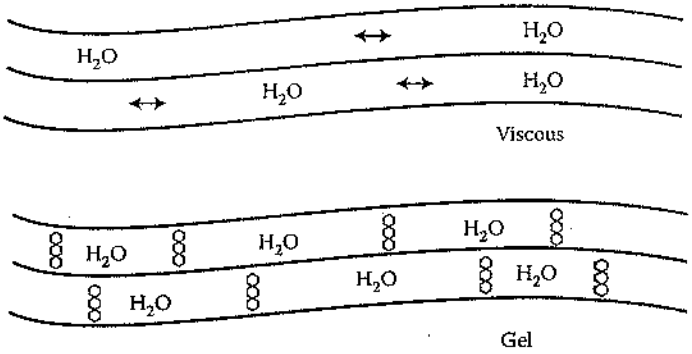

FIGURE 8.2 Viscous and gel-forming linear polymers. This shows drawings representing viscous linear polymers (top) and gel-forming linear polymers (bottom). Long-chain linear polymers orient parallel to adjacent fibers and increase viscosity in a concentration-dependent manner. Some long-chain linear polymers also can form cross-links that create a gel in a concentration-dependent manner. (Drawings recreated with permission from John D. Keller, Jr., Keller Konsulting LLC, Freehold, NJ. With permission.)

(Figure 8.1). The irregular branches make it difficult for the polymer molecules to pack in a regular array and, therefore, highly branched polymers have little effect on viscosity. Viscosity is a function of the volume of a molecule as it rotates in water (effective hydrodynamic size). The volume "swept out" by a fully extended linear fiber is much greater than a fiber with an equal number of sugar units (same molecular weight) but with a "bush-like," highly branched configuration (Figure 8.1). As the volume occupied by a polymer molecule is a function of the radius-cubed, even a small increase in effective hydrodynamic size can translate into a large increase in viscosity. Straight chain viscous polymers that have the added ability to form cross-links with adjacent polymers also can form a gel (behave as a visco-elastic solid) (Figure 8.2). Both viscosity and gel formation are concentration-dependent phenomena. Gel-formation is an important driver of several metabolic health benefits for dietary fiber supplements, including cholesterol lowering, improved glycemic control, weight control and stool normalization (soften hard stool in constipation and firm loose/liquid stool in diarrhea). Note that molecular weight is often used as a correlate of viscosity and/or gel-formation, but this is not always accurate unless one is comparing within the same fiber (e.g., high molecular weight β-glucan versus low molecular weight β-glucan). Correlating molecular weight and viscosity across fiber types can lead to an erroneous conclusion if one fiber type is linear and one is highly branched. As described above, a linear polymer can have a significant effect on viscosity proportionate to its molecular weight (e.g., β-glucan), whereas a highly branched "bush-like" polymer (Figure 8.1) with a similar molecular weight may have little/no significant effect on viscosity (e.g., wheat dextrin, inulin).

A recent study [17] quantified the viscosity of select dietary fibers (soluble and insoluble) at various concentrations. The results showed that the viscosity of all fiber solutions was concentration-dependent and shear rate-dependent. Insoluble fibers (rice bran, soy hulls, and wood cellulose) exhibited the lowest viscosities ("non-viscous"), whereas soluble viscous, gel-forming fibers (guar gum, psyllium, and xanthan gum) exhibited the highest viscosities [17]. Guar gum, psyllium, and oat bran (all soluble fibers) were highly viscous, gel-forming fibers indicating a potential for these fibers to exhibit blood glucose and cholesterol lowering benefits in man. In contrast, wheat bran, rice bran, and wood cellulose (all insoluble fibers), under conditions simulating the small intestine, did not exhibit an ability to raise viscosity or form a gel, indicating that these fibers would not be expected to have a significant effect on blood glucose and cholesterol lowering. Note that there are only two fiber supplements that are recognized by the United States FDA for reducing the risk of cardiovascular disease by lowering serum cholesterol: β-glucan (from oats and barley) and psyllium [22]. Both are soluble, gel-forming fibers. As the following sections will demonstrate, when assessing viscosity/gel-forming-dependent health benefits like cholesterol lowering and improved glycemic control, insoluble fiber (e.g., wheat bran), low viscosity soluble fiber (acacia gum/gum Arabic, low molecular weight β-glucan), and non-viscous soluble fibers (e.g., wheat dextrin, inulin) have no appreciable effect on viscosity/gel-dependent health benefits, and can be/have been used as negative controls (placebo) in these studies [16,21,23–25].

8.2.1 FERMENTATION

By definition, fiber supplements must be resistant to digestion in the stomach and small intestine, arriving in the proximal large intestine (cecum) relatively intact. The large intestine is home for 10^{11}–10^{12} bacteria per milliliter, approximately 10-times the number of cells in the human body [26,27]. These bacteria are capable of feeding on most fiber supplements to varying degrees. The terms "fermentable" and "non-fermentable" are used to describe whether a fiber supplement can be degraded (fermented) by the bacteria residing in the intestines. Some fiber supplements are readily fermented (e.g., inulin, wheat dextrin, β-glucan, guar gum), some are only partially/poorly fermented (e.g., wheat bran), and some are not fermented (e.g., methylcellulose, psyllium). Non-fermented and poorly fermented fiber supplements pass through the gastrointestinal tract largely unchanged. Readily fermented fiber supplements can be rapidly degraded by bacteria in the proximal large bowel, and the bacteria can use the degradable fiber as an energy source, leading to an increased biomass. Byproducts of fermentation include short-chain fatty acids (SCFAs; acetate, propionate, and butyrate) and gas [28]. Butyrate provides a preferred energy source for colonic mucosal cells. SCFAs also can be absorbed by the large intestine, providing harvested energy as a calorie source for the host. It is important to note that this energy harvest by the host means that many fiber supplements are not calorie-free, which may affect their ability to provide a long-term weight benefit.

Intestinal gas produced by fermentation is eliminated from the bowel by one of two mechanisms: it is absorbed into the blood stream and exhaled by the lungs, objectively measured in a breath gas analysis; or it is expelled as flatulence, objectively assessed by volume and content of expelled gas, and subjectively assessed as frequency of episodes and odor [29,30]. The vast majority of gases in the human gut are nitrogen (N_2), oxygen (O_2), hydrogen (H_2), carbon dioxide (CO_2), and methane

(CH_4) [29,31]. These gases are odorless and comprise more than 99% of intestinal gas. The unpleasant odors that can accompany intestinal gas are the result of trace gases that contain sulfur, such as hydrogen sulfide (H_2S) [29]. In the intestines, frequent low amplitude, rapidly propagating contractions propel gas toward the anus more rapidly than higher viscosity substrates like solid stool, which is propelled by infrequent (approximately six per day) high amplitude propagating contractions [32]. Consistent with the high frequency, low amplitude and high rate of propagation of these small, rapidly propagating contractions, gas can transit the entire gastrointestinal tract in less than 1 h [32]. In contrast, solids may take 1–2 days. Flatulence episodes also occur far more frequently (14/day) [32,33] than bowel movements (1–2 per day), consistent with their relative speed of transport through the gut.

Much of what is known about the relative degree of fermentation of various fibers has been gleaned from *in vitro* testing. *In vitro* testing is used as a model, designed as an inexpensive and rapid method to predict what *could* happen in the human intestinal tract. As with all models, however, the technique has limitations. For instance, for many years psyllium has been considered fermentable based on *in vitro* techniques for assessing fermentation [34–36]. There is a significant discrepancy, however, between *in vitro* data and human (clinical) experience with psyllium. Psyllium, a soluble viscous, gel-forming fiber, can be fermented under *in vitro* test conditions because samples are diluted and homogenized with a high-speed mechanical blender [34–36]. Exposure of the hydrated/gelled psyllium to the rapid shearing forces of a high-speed blender will destroy the physical structure of the gel matrix, artificially rendering psyllium fermentable by destroying the steric hindrance that would otherwise physically impede enzymatic degradation (steric protection). In contrast to the *in vitro* results, there are five published, well-controlled clinical studies, which show that psyllium is not fermented in the human gut [37–41]. The five clinical studies assessed the fermentation of psyllium versus a negative control (placebo), a positive control (lactulose), and/or comparative fibers (e.g., methylcellulose, guar gum, pectin, cellulose) using assessments for both of the mechanisms by which the gut handles gas: breath gas analysis that assesses intestinal gas that has been absorbed into the blood stream and expelled via the lungs, and flatulence, which assesses gas expelled via the anus [37–41]. For example, a randomized, blinded, two-period cross-over design study assessed a high-dose of psyllium (18 g/day) versus placebo for breath gas production (accepted marker for degree of fermentation) [41]. The study showed that breath hydrogen was directionally higher for placebo (38.6 ml/h) than for the high-dose psyllium (23.8 ml/h). There was no significant difference in bacterial dry mass for either test product (indicative of no increase in biomass due to fermentation), and there was no difference in reported symptoms, though the mean score for flatulence was directionally higher for placebo (9.3) than for psyllium (6.1) [41]. Another study, a randomized, blinded, three-way cross-over design assessing high doses of guar gum (20 g/day), psyllium (20 g/day), and control (polysaccharide-free diet), showed that guar gum was readily fermented compared to placebo, but psyllium was not fermented [37]. Assessments of breath methane were identical for psyllium (20 ppm) and placebo (20 ppm), but significantly higher for guar gum (37 ppm). Additionally, serum acetate increased significantly for guar gum, but decreased versus baseline for both psyllium and placebo [37]. In a third study, a double-blind, randomized, placebo-controlled design with 108 subjects who believed their "gas" symptoms (increased flatulence and bloating) were caused by ingestion of fiber, subjects were given doses of placebo 10 g, psyllium 3.4 g, methylcellulose 2 g, or lactulose 5 g (readily fermented) [39]. The lactulose group passed gas significantly more often than did the psyllium or methylcellulose groups ($p < 0.01$). Psyllium was not different from baseline or placebo for passing gas, or any other symptom [39]. Another study included 25 healthy volunteers and assessed the effects of diets supplemented with 10 g psyllium, methylcellulose, or lactulose versus placebo for reports of "gaseous" symptoms, including number of flatulence episodes, impression of increased rectal gas, and abdominal bloating [38]. Five of the subjects were also assessed for breath hydrogen excretion. The results showed that participants passed gas an average of 10 times per day during the placebo period. A significant increase in gas passages (19 times/day) and a subjective impression of increased rectal gas were reported with lactulose, but not with either of the two fiber preparations. Breath hydrogen excretion did not increase after ingestion of either of the fiber supplements. In contrast, a significant ($p < 0.05$) increase in feelings of abdominal bloating, which subjects perceived as "excessive gas", was reported with lactulose and both fiber supplements. The authors concluded that clinicians should distinguish between excessive rectal gas, which indicates excessive gas production, and feelings of bloating, which are usually unrelated to excessive gas production [38]. They recommended that treatment of excessive rectal gas consists of limiting the supply of fermentable substrates to the colonic bacteria (e.g., fermentable fibers). Symptoms of bloating without evidence of excessive rectal gas may be indicative of IBS [38]. Considering together, five clinical studies provided congruent results: objective measures of breath gas, and subjective assessments of flatulence episodes (the two mechanisms by which gas is handled in the large bowel), showed that psyllium did not increase intestinal gas. Two of these studies also assessed SCFA production [37,41]. The first study, in which subjects were fed a low fiber diet (6 g dietary fiber/day and 1–2 g resistant starch/day), showed that three of six SCFAs increased with psyllium consumption [41]. The study also showed significant increases in arabinose and xylose (the sugars that comprise psyllium), recovered in a highly polymerized form, confirming that the psyllium gel transited the large bowel intact. In contrast to the first study, the second study, in which subjects were fed a polysaccharide-free diet, showed no increase in SCFAs with psyllium dosing, supporting that psyllium is not fermented in the large bowel [37]. The SCFA increase noted in the first study was likely due to residual nutrients captured in the gel matrix and carried into the large bowel, but the amount was insufficient to be detected on breath gas analysis [37]. On the basis of these five published clinical assessments of gas production and SCFA production, it is reasonable to conclude that the psyllium gel remains intact throughout the large bowel, and is not fermented in the human gut. The data further support that *in vitro* assessments of fermentation may not always be predictive of the human experience for gel-forming fibers.

An emerging area of research is exploring the effects of fermentable fibers, some of which are prebiotics that can provide a preferred food source for specific "healthy" bacteria (typically lactic acid-producing bacteria like bifidobacteria and lactobacilli), thereby increasing the number of these bacterial species present in the large bowel [42]. A "prebiotic" has been defined as "a selectively fermented ingredient that allows specific changes in the composition and/or activity in the intestinal microflora that confers benefits upon host well-being and health" [42]. While this continues to be an area of emerging science, regulatory bodies do not yet recognize a correlation between increasing the numbers of specific gut bacteria and a clinically meaningful health benefit. The European Food Safety Authority concluded that the available clinical evidence does not establish that increasing numbers of gastrointestinal microorganisms is a beneficial physiological effect [43]. The panel further concluded that a cause and effect relationship has not been established between the consumption of prebiotics and a beneficial physiological effect related to increasing numbers of gastrointestinal microorganisms [43]. Similarly, the Dietary Guidelines for Americans 2010 Committee (DGAC) conducted a review that included prebiotics [44]. Though the DGAC believed that gut microflora play a role in health, and investigation of the gut microflora is an important emerging area of research, they concluded that there was insufficient evidence to make dietary recommendations for Americans regarding prebiotics.

8.3 PHYSICAL EFFECTS OF FIBER SUPPLEMENTS IN THE STOMACH

Anatomically, the stomach is divided into four regions (cardiac, fundus, corpus, and pyloric antrum), but functionally the stomach has only two regions: proximal (storage) and distal (antral pump) [5]. The proximal region of the stomach has rugae, accordion-like folds that can relax and stretch to accommodate a meal (Figure 8.3). When stretched (filled), the proximal stomach exerts a tonic contraction that gradually forces food into the distal portion of the stomach, where rugae give way to a smooth-walled, muscular tube called the gastric antrum (upper right corner of

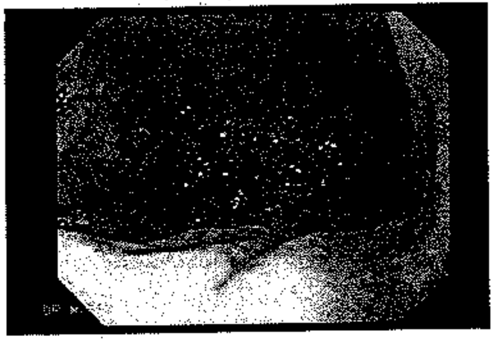

FIGURE 8.3 Endoscopic view of rugae in the proximal stomach. This is an endoscopic view of the proximal stomach. Note the mucosal folds (rugae) that allow for expansion of the proximal stomach to accommodate a meal. During the fed state, after relaxing to accommodate the meal, the proximal stomach provides tonic pressure to gradually push food toward the distal stomach. In the upper right corner of this endoscopic view, the rugae give way to a smooth-walled muscular tube (antrum), known as the "antral pump." (Reprinted with permission from Julio Murra-Saca, Chief of Department of Gastroenterology, Hospital Centro de Emergencias; El Salvador Atlas of Gastrointestinal Video Endoscopy.)

Figure 8.3). In the gastric antrum, phasic waves of contraction, known as the "antral pump," start in mid-stomach and move as a ring of contraction toward the duodenum (Figure 8.4), driving discreet boluses of gastric contents toward the pyloric sphincter [5]. The pyloric sphincter, which is normally closed (Figure 8.4a), acts at the primary gate for controlling the rate of gastric emptying. During the fed state (food in the stomach), the pyloric sphincter transiently opens (only 1–2 mm) at the beginning of an antral wave of contraction, and the progressive wave of contractions forces small boluses of liquid and small food particles (less than 2 mm) through the pyloric sphincter, into the duodenum [45]. Partially through the antral contraction, the pyloric sphincter closes, blocking the exit of gastric contents and causing pressure to build between the advancing wave of contraction and the closed pyloric sphincter. The trapped digesta is forced to "back-extrude" through the advancing fist-like wave of contraction (Figure 8.4b). This back extrusion under pressure is the grinding action of the stomach, mechanically shearing large food particles into smaller ones, and mixing food with gastric acid and pepsin (an enzyme that degrades proteins into peptides). The rate of gastric emptying is controlled by several factors, including caloric density (low calorie digesta empties faster than high calorie digesta) and meal composition (liquids empty faster than solids; low viscosity empties faster than high viscosity) [5]. The first line (immediate) control of gastric emptying is the small size of the pyloric sphincter opening (1–2 mm). A secondary control mechanism is the feedback mechanism between the duodenum and stomach that senses caloric density. A more delayed mechanism that affects the rate of gastric emptying is the "ileal brake" phenomenon. Nutrients are normally absorbed early in the small bowel. If nutrients are captured in the gel-matrix of a viscous, gelling fiber, they can be

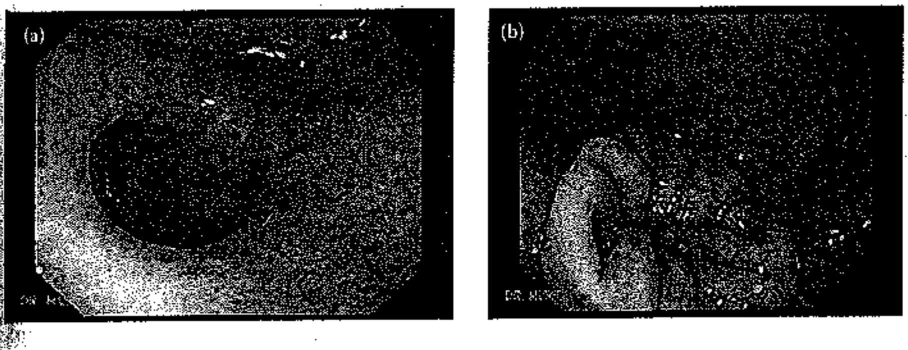

FIGURE 8.4 Endoscopic view of a peristaltic wave of contraction in the gastric antrum. This shows two endoscopic views of the distal stomach (antrum). (a) A wave-like contraction can be seen moving toward the pyloric sphincter. Early in the contraction, which is not yet lumen-occluding, the pyloric sphincter is open (1–2 mm) to allow liquids and small food particles to exit the stomach under low pressure. Mid-way through the contraction, the sphincter closes (arrow). As the peristaltic wave of contraction progresses, it becomes lumen-occluding, and gastric contents become trapped between the closed pyloric sphincter and the "fist-like" wave of contraction (b), which provides the grinding action of the stomach. (Reprinted with permission from Julio Murra-Saca, Chief of Department of Gastroenterology, Hospital Centro de Emergencias; El Salvador Atlas of Gastrointestinal Video Endoscopy.)

delivered to the distal ileum where nutrients are not usually present, stimulating a cascade of feedback mechanisms that slow gastric emptying and small bowel transit to reduce/prevent loss of nutrients to the large bowel, and release peptides that have several metabolic effects important to glycemic control (discussed in the section on small bowel effects) [5].

Published data on the effects of fiber supplements on gastric emptying show mixed results, which may be due in large part to the different methods used to assess gastric emptying. For example, if a soluble viscous/gel-forming fiber is added to a liquid test meal (e.g., glucose tolerance test), the increased viscosity provided by a gel-forming fiber would tend to slow the rate of gastric emptying [46]. In contrast, if a viscous soluble fiber is added to a solid test meal, the apparent rate of gastric emptying may not be significantly altered. For example, guar gum slows gastric emptying to a greater extent when given with a liquid meal than with a solid meal [47]. Additional studies show that guar gum and psyllium, both soluble viscous/gel-forming fibers, had no significant effect on gastric emptying when combined with a solid test meal [48] or a semi-solid test meal [49]. The observable effects of a fiber supplement on gastric emptying may also be tied to the duration of the dosing period in the study. Most studies assess gastric emptying after a single dose of fiber. A longer-term study assessed the effects of sustained fiber ingestion on gastric emptying in healthy volunteers placed on a low-fiber (3 g) diet for 2 weeks, followed by 4 weeks of an isocaloric diet supplemented with 20 g/day of either apple pectin (soluble viscous fiber) or cellulose (insoluble fiber used as a placebo) [50]. At the conclusion of each test period, subjects ingested a technetium-labeled low-fiber test breakfast. The study showed that gastric emptying was prolonged approximately two-fold after pectin supplementation ($p < 0.005$), but cellulose supplementation did not alter the rate of gastric emptying. Taken together, these data show that fiber supplements can have an effect on the rate of gastric emptying, but the outcome may be significantly affected by the study techniques employed, and the duration of the study. It should also be noted that a fiber-induced change in the rate of gastric emptying is a *mechanism* that could be a contributing factor associated with a health benefit, but an alteration in the rate of gastric emptying should not be construed as direct evidence of a clinically meaningful health benefit.

The above studies assessed an early or "immediate" effect on gastric emptying, which is primarily a function of restricted flow through the small (1–2 mm) opening in the pyloric sphincter, and calorie density (duodenal feedback). Another technique that has been used to assess the rate of gastric emptying is time to peak excretion in a 13-C breath-gas analysis. In a cross-over study, a labeled (13-C) liquid test meal (200 mL) was administered alone (control) or with 6, 12, or 18 g of psyllium fiber (soluble viscous, gel-forming, non-fermented fiber) [51]. Breath samples collected over a 4-h period showed a statistically significant, dose-dependent increase in time to peak excretion (54.5 min for control to 93.3 min for 18 g of psyllium), which was interpreted as a dose-dependent delay in gastric emptying. What is unclear, however, is the degree to which this delay in absorption is directly attributable to gastric emptying versus a viscosity-dependent delay in nutrient absorption in the small bowel. Also, note that psyllium *slowed* absorption of the liquid test meal/label, but did not change the *total* absorption of nutrients/label (assessed as area under the curve). In an earlier study that assessed the effects of the pectin (15 g) on gastric emptying and blood glucose concentration, the viscous soluble fiber slowed gastric emptying when added to both liquid and solid test meals, but only affected peak postprandial glucose concentration with the liquid test meal [52]. This suggests that the observed immediate (first hour) delay in gastric emptying with both test meals was not the mechanism driving the immediate (first hour) change observed in postprandial glucose, which was observed only with the liquid test meal. The data suggest that pectin increased the viscosity of chyme in the small bowel, thereby slowing nutrient absorption. Similarly, a placebo-controlled study that assessed the effects of psyllium (7.4 g) on gastric emptying, feelings of hunger and energy intake in 14 normal volunteers, showed that there was no psyllium-induced delay in gastric emptying, yet feelings of hunger and measures of energy intake were significantly lower with psyllium versus placebo (13 and 17% lower, respectively; $p < 0.05$) [53]. Postprandial increases in serum glucose, triglycerides, and insulin concentrations were also lower with psyllium versus placebo ($p < 0.05$). Considered together, these data support that, while a delay in gastric emptying could be a mechanism that supports a health benefit like improved glycemic control, it is apparent that a mechanism other than delayed gastric emptying is exerting a significant effect on viscous/gel-forming fiber-induced increases in satiety, decreases in energy intake, and decreases in postprandial measures of blood glucose. In conclusion, the data on the effects of fiber supplements on gastric emptying can vary depending on the study techniques used, and are not always well-correlated with a measurable health benefit.

8.4 PHYSICAL EFFECTS OF FIBER SUPPLEMENTS IN THE SMALL INTESTINE

8.4.1 Importance of Gel-Formation in the Small Intestine

The small intestine is approximately 7 meters long and divided anatomically into 3 regions: duodenum, jejunum, and ileum. The mucosa of the small intestine is studded with millions of small villi (Figure 8.5), each covered with approximately 1000 microvilli per 0.1 micron^2, making the small intestine the largest body surface exposed to the outside world (approximately 250 m^2, roughly the size of a tennis court) [5,54]. Delivery of acidic nutrients into the duodenum (proximal small bowel) stimulates the gall bladder to contract and release bile, and stimulates pancreatic secretion (inorganic = water, bicarbonate and electrolytes; organic = digestive enzymes). The total quantity of fluid absorbed by the small bowel each day is a combination of fluids consumed (about 1.5 L/day) and the digestive juices secreted (about 6 to 7 L/day). In the fed state, the motor activity of the small bowel predominantly consists of segmental (mixing) contractions [5,54]. These segmental contractions mix chyme back and forth, exposing food particles to digestive enzymes and bile, and facilitating exposure of digested nutrients to the absorptive brush border of the mucosa for absorption. Chyme, the liquid contents of the small intestine, is normally very low in viscosity, and is easily mixed with digestive enzymes for degradation and absorption of nutrients. The very large surface area of the mucosa results in efficient absorption of nutrients, which normally occurs early in the proximal

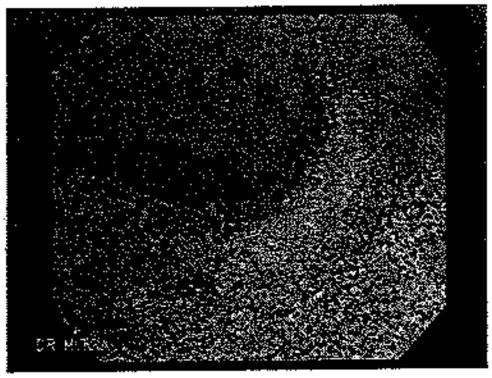

FIGURE 8.5 Endoscopic view of the mucosal villi of the small intestine. This shows an endoscopic view of the mucosa of the small intestine. Note that the mucosa is studded with millions of small villi, each covered with approximately 1000 microvilli per 0.1 micron^2. The large surface area of the small intestine (roughly the size of a tennis court) allows for efficient absorption of nutrients, which is normally accomplished early in the proximal regions of the small bowel. (Reprinted with permission from Julio Murra-Saca, Chief of Department of Gastroenterology, Hospital Centro de Emergencias; El Salvador Atlas of Gastrointestinal Video Endoscopy.)

small bowel (Figure 8.6) [5,54]. Introduction of insoluble fiber (e.g., wheat bran) or soluble non-viscous fiber (e.g., inulin, wheat dextrin) has no significant effect on the rate of nutrient absorption in the small bowel. In contrast, introduction of a soluble, viscous, gel-forming fiber (e.g., guar gum, psyllium, high molecular weight β-glucan) significantly increase the viscosity of chyme in a dose-dependent manner, which slows the mixing of chyme and slows the interactions of digestive enzymes with nutrients. This results in a slowing of the degradation of complex nutrients into simple, absorbable components, all of which slows the absorption of glucose and other nutrients (Figure 8.6) [5]. This slowing of nutrient degradation and absorption also can lead to delivery of nutrients to the distal ileum, where nutrients are not normally present (Figure 8.6). Nutrients in the distal ileum stimulate mucosal receptors to initiate several metabolic responses, one of which is the release of glucagon-like peptide 1 (GLP-1) into the blood stream. GLP-1 is a short-lived (approximately 2-min half-life) peptide that significantly decreases appetite, increases insulin secretion, decreases glucagon-secretion [a peptide that stimulates glucose production in the liver], increases pancreatic β-cell growth (cells that produce insulin), improves insulin production and sensitivity, and slows gastric emptying and small bowel transit via a feedback loop called the "ileal brake" phenomenon [5]. Considered together, the viscosity/gel-related mechanisms for improved glycemic control include: lowering of the glycemic index of ingested foods, increasing the viscosity of chyme to slow glucose absorption and starch degradation in the small bowel, and hormonal responses to delayed nutrient absorption [18,56–58]. All of these phenomena lead to a viscosity/gel-dependent improvement in glycemic control for patients with type 2 diabetes, and those at risk for developing the disease (e.g., metabolic syndrome) [5,18,59–65].

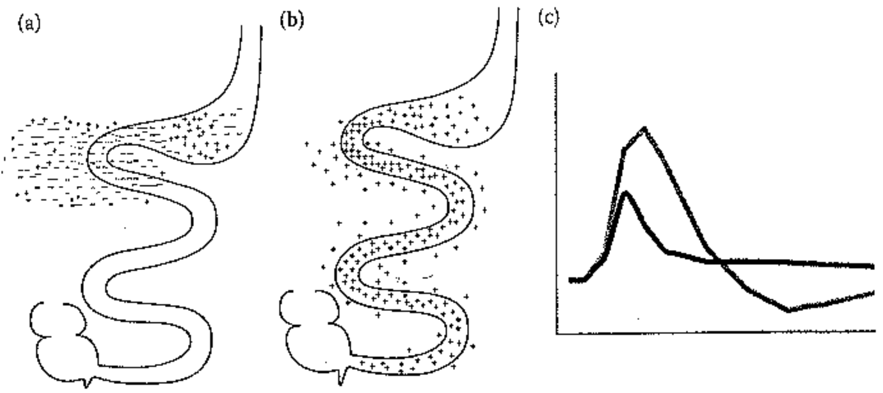

FIGURE 8.6 Absorption of nutrients in the small bowel is delayed by viscous fiber. This shows diagrams of nutrient absorption in the small bowel. Nutrients normally absorb very early in the proximal small bowel (a). Introduction of a viscous, gel-forming fiber (e.g., guar gum, psyllium, high molecular weight β-glucan) can delay nutrient absorption to more distal regions of the small bowel (b). Respective blood glucose concentrations reflect the rate of absorption in the small bowel (c). Rapid nutrient absorption (c: gray line, corresponds with (a)) is reflected by the higher peak concentration of blood glucose followed by a transient hypoglycemic trough below baseline. With the introduction of a viscous, gel-forming soluble fiber, the delay in nutrient absorption (c: black line, corresponds with (b)) results in an attenuation of glucose excursions: lower peak concentration of blood glucose, and attenuated hypoglycemic trough. The viscous/gel-forming fiber-related delay in nutrient absorption does not result in a significant difference in total nutrient absorption. (Drawings recreated with permission from Thomas Wolever, Ph.D, University of Toronto.)

Another health benefit of fiber associated with small bowel absorption is the lowering of elevated serum cholesterol concentrations, specifically low-density lipoprotein (LDL)-cholesterol. An example of this viscosity/gel-related effect is shown in a double-blind, parallel-design, multicenter clinical study that randomly assigned 386 subjects to receive cereal containing wheat fiber (negative control) or one of three oat bran cereals (high, medium, and low viscosity), equaling 3–4 g of β-glucan daily [23]. The viscosity of the cereals was altered by the degree of processing (heat and pressure) to which the fiber was exposed while making the cereal. The results showed that cholesterol lowering was highly correlated with the viscosity of the gel-forming fiber: high viscosity was correlated with significant cholesterol lowering; low viscosity was correlated with diminished cholesterol lowering. The study clearly demonstrated that the physiochemical properties of oat β-glucan were altered by processing, and the degree to which a fiber is processed before marketing should be considered when assessing the cholesterol-lowering ability of an oat-containing product. It should be noted that this study was performed with a gel-forming fiber, and the altered viscosity of the gel-forming fiber was correlated with efficacy. This does not, however, imply that simple viscosity, without gel-formation, is highly correlated with cholesterol lowering. This observation was highlighted in a placebo-controlled, randomized, parallel study of 105 patients with hypercholesterolemia that assessed the cholesterol-lowering effects of a high viscosity, gel-forming soluble fiber (psyllium) versus a viscous but non-gel-forming soluble fiber (methylcellulose) and a synthetic soluble viscous fiber (calcium polycarbophil) dosed three times a day for 8 weeks [66]. The results showed that LDL-cholesterol concentrations versus placebo were significantly lower for the gel-forming psyllium treatment group (−8.8%, $p = 0.02$), but the non-gel-forming methylcellulose and calcium polycarbophil failed to show a significant reduction in LDL-cholesterol [66]. It should be noted that raw polycarbophil is a gel-forming synthetic fiber, but the commercially available version is a calcium salt, a formulation intended to prevent gel-formation with swallowing (reduction in the risk for choking). This formulation depends on the assumption that the calcium will dissociate from the polycarbophil in the gut, allowing it to form a gel. A preclinical study, however, showed that while raw polycarbophil had a significant stool softening effect, the calcium polycarbophil formulation was not different from placebo [67]. Both the clinical cholesterol-lowering study and the preclinical stool softening study support that the calcium does not significantly dissociate from the polycarbophil in the gut, leaving the fiber inactive (non-gel-forming). Another example of the importance of gelling is raw guar gum, which is a highly viscous, gel-forming soluble fiber with proven viscosity/gel-related health benefits. The commonly marketed version of guar gum, however, is a "partially hydrolyzed guar gum" (PHGG) which, depending on the degree of hydrolysis, is non-gel-forming to improve palatability ("dissolves completely in water with no viscosity"). This non-viscous version will not provide the viscosity/gel-dependent health benefits associated with the original, gel-forming raw guar gum [68]. Considered together, these observations emphasize the importance of being cognizant of not only the specific fiber types that exhibit characteristics closely associated with specific health benefits, but also the degree of processing to which the final marketed products have been exposed. For a simple and reasonable test to determine if a fiber supplement can provide viscosity/gel-related health benefits, stir a single dose of the marketed product (usually 2–4 g fiber) into 120 mL of water, and let it sit for 15 min. If the fiber supplement does not readily dissolve in the water, then form a viscous gel within the allotted time, it is unlikely to have a clinically meaningful effect on cholesterol lowering, improved glycemic control, appetite control, or other viscosity/gel-related health benefits.

8.5 SMALL INTESTINE: CLINICAL DATA SUPPORT AN "IMPROVED GLYCEMIC CONTROL" HEALTH BENEFIT FOR GEL-FORMING SOLUBLE FIBER SUPPLEMENTS

There are two primary methods to assess the effects of fiber supplements on glycemic control. The first is an acute test on postprandial blood glucose concentrations (glucose tolerance test) in which a glucose load (e.g., 50 g glucose solution) is administered alone or with a fiber supplement (Figure 8.6). Blood glucose concentrations are drawn at frequent, pre-determined intervals over a few hours to assess the rate of glucose absorption. Glucose is normally rapidly absorbed, resulting in a relatively fast rise in blood glucose leading to a high peak concentration, followed by a relatively rapid decline, with a transient excursion below the baseline level (Figure 8.6a and c). This transient hypoglycemia is due to a rapid rise in insulin, which tends to stay elevated past the point where the blood glucose concentration has returned to baseline, resulting in transient hypoglycemia. It has been established for over three decades that the viscosity of a gel-forming dietary fiber is highly correlated with reducing postprandial glucose and insulin serum concentrations. In a study published in 1978 [68], volunteers underwent glucose (50 g) tolerance tests with and without the addition of several fiber supplements, including guar gum. Native guar gum is a highly viscous, gel-forming fiber, and it was effective in significantly lowering both postprandial blood glucose and insulin concentrations. This beneficial response, however, was abolished when the guar gum was hydrolyzed (to a non-viscous form). The study showed that a reduction in postprandial blood glucose was highly correlated with viscosity ($r = 0.926$; $p < 0.01$), and a slowing of mouth-to-cecum transit time ($r = 0.885$; $p < 0.02$). This means that high viscosity, gel-forming fiber supplements (e.g., psyllium, high molecular weight β-glucan, raw guar gum) can provide a clinically meaningful effect on elevated blood glucose, but non-viscous soluble fiber supplements (e.g., wheat dextrin, inulin) do not alter viscosity or provide a clinically meaningful glycemic benefit [4,5]. Note that the study above [68] was conducted with a gel-forming fiber, and the results stem from alteration of the viscosity of this gel-forming fiber. These data should not be construed to support a health benefit for viscosity alone, without cross-linking of fiber molecules to form a gel. All of the fiber supplements shown to improve glycemic control in patients with type 2 diabetes are gel-forming fibers.

Patients with type 2 diabetes have an impaired sensitivity to insulin and/or a decreased insulin output, resulting in an exaggerated elevation in peak postprandial glucose concentrations. An effective fiber supplement will delay glucose absorption, lowering the peak blood glucose concentration and attenuating the hypoglycemic excursion below baseline without significantly affecting total nutrient absorption (area under the curve; Figure 8.6b and c). Note that postprandial glucose studies should only be considered as a diagnostic tool for assessing patients at risk for diabetes, and a mechanistic tool for assessing the acute effects of fiber on glucose absorption. These single-meal studies do not necessarily predict a longer-term metabolic health benefit, such as improving glycemic control in type 2 diabetes. For example, acute postprandial studies of the effects of viscous fiber can show an attenuation of peak postprandial blood glucose concentrations in healthy subjects with normal glycemic control [69–72], while longer-term studies (weeks or months) do not show a reduction in the already normal blood glucose concentration of healthy subjects with normal glycemic control [73–75]. Fiber supplements will not cause hypoglycemia in healthy subjects or subjects with compromised glycemic control because suppression of glucagon by GLP-1 does not occur at hypoglycemic levels (feedback mechanism) [5]. The longer-term effects of an effective soluble viscous, gel-forming fiber on fasting blood glucose concentrations are proportional to baseline glycemic control: no significant effect on normal blood glucose concentrations in healthy subjects [73–75], a moderate effect in patients with pre-diabetes and metabolic syndrome [e.g., −19.8 mg/dL for psyllium 3.5 g bid; −9 mg/dL for guar gum 3.5 g bid] [76] and a larger effect in patients with type 2 diabetes (e.g., psyllium, −35.0 mg/dL [77] to −89.7 mg/dL [78]).

Recall that nutrients are normally absorbed early in the small bowel. Delaying the degradation and absorption of nutrients in the small bowel, leading to release of metabolically active peptides from the distal ileum, is a viscosity/gel-driven phenomenon that is not exhibited by insoluble fiber supplements (e.g., wheat bran). Similarly, there is a paucity of clinical data supporting that marketed soluble nonviscous fiber supplements (e.g., inulin, wheat dextrin), or marketed soluble viscous, non-gel forming fiber supplements (e.g., methylcellulose) exhibit a clinically meaningful, long-term effect on glycemic control at physiologic doses. To appropriately assess the long-term benefits of a soluble viscous/gel-forming fiber in subjects with impaired glycemic control, studies should include multiple daily pre-meal doses of a fiber supplement (so the fiber becomes mixed with the meal), and the assessment period should be two or more months to allow for a meaningful assessment of hemoglobin-A1c (HbA1c). HbA1c is a form of hemoglobin that becomes glycated over time, reflecting average plasma glucose concentrations over several months. As average blood glucose increases, the fraction of glycated hemoglobin increases, serving as a marker for elevated blood glucose exposure over the previous several months. Numerous multi-month clinical studies have demonstrated that consumption of a soluble, viscous/gel-forming fiber (e.g., psyllium, raw guar gum, high molecular weight β-glucan) before meals can improve glycemic control (lowers fasting blood glucose, insulin, and HbA1c concentrations) in subjects at risk for type 2 diabetes (e.g., metabolic syndrome) and in patients being treated for type 2 diabetes [4,5,23,76–89].

An example of a gel-forming fiber demonstrating long-term improved glycemic control is a double-blind, placebo-controlled clinical study designed to evaluate the effects of two doses of psyllium on fasting blood glucose and HbA1c in 37 patients already being treated (prescription hypoglycemic medications) for type 2 diabetes mellitus [82]. In this study, patients were randomly assigned to one of three treatment groups: a relatively low dose of psyllium (3.4 g twice a day), a higher dose psyllium (6.8 g twice a day), or placebo. All doses were consumed just prior to breakfast and dinner, to allow for mixing with food. The study was 20 weeks in duration (8 weeks baseline, 12 weeks treatment). Results show that psyllium treatment provided a statistically significant ($p < 0.05$) lowering of fasting blood glucose concentrations (versus placebo) at treatment weeks 4, 8, and 12 (Figure 8.7a) that was directionally dose-responsive (Figure 8.7a). The results were similar for HbA1c (Figure 8.7b). Note that the improvement in glycemic control observed with both doses of psyllium was above that already conferred by a restricted diet (all patients) and a stable dose of a sulfonylurea (81.1% of patients) [82].

In summary, when considered across studies, the effects of a viscous, gel-forming fiber supplement (e.g., raw guar gum, psyllium, high molecular weight β-glucan) on glycemic control are heavily influenced by the baseline fasting blood glucose concentrations (e.g., degree of loss of glycemic control): no effect on normal fasting blood glucose concentrations, a moderate effect on moderately elevated fasting blood glucose concentrations, and a markedly greater effect in patients with significantly elevated fasting blood glucose concentrations. It is important to note that consumption of viscous, gel-forming fiber supplements will not cause blood glucose concentrations to drop below normal limits (hypoglycemia), because the suppression of glucagon by GLP-1 does not occur at hypoglycemic levels. When initiating an effective fiber therapy in patients already being treated for diabetes with prescription drugs, however, it is important to monitor blood glucose concentrations, as an

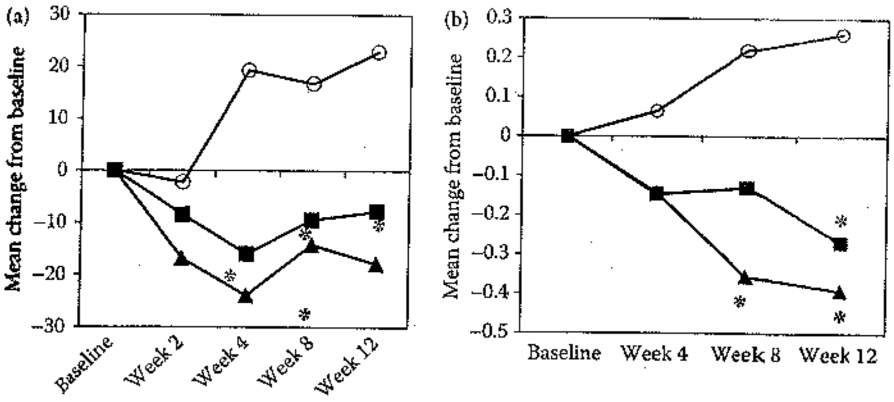

FIGURE 8.7 Psyllium lowers fasting blood glucose and HbA1c in patients with type 2 diabetes. (a) A graph of fasting blood glucose concentration (mg/dL) as a response to treatment. Both doses of psyllium significantly ($p < 0.05$) lowered fasting blood glucose compared to placebo at weeks 4, 8, and 12 (placebo = circle; psyllium 3.4 g BID = square; psyllium 6.8 g BID = triangle). (b) A graph of HbA1c (%) as a response to treatment. Pysllium 6.8 g BID significantly ($p < 0.05$) lowered HbA1c compared to placebo at week 8, and both doses of psyllium significantly ($p < 0.05$) lowered HbA1c compared to placebo at week 12 (placebo = circle; psyllium 3.4 g BID = square; psyllium 6.8 g BID = triangle). (Reprinted with permission from Feinglos, M. et al. 2013. *Bioact Carbohydr Diet Fibre.* 1, 156–161.)

effective gel-forming fiber co-therapy may decrease the required doses of the prescription hypoglycemic drugs. Insoluble fiber (e.g., wheat bran), soluble non-viscous fiber (e.g., inulin, wheat dextrin), and soluble viscous non-gel forming fiber (e.g., methylcellulose) have no significant glycemic benefit, and have been used as placebo controls in clinical studies of soluble viscous, gel-forming fibers.

8.5.1 SMALL INTESTINE: REDUCED RISK OF CARDIOVASCULAR DISEASE BY LOWERING SERUM CHOLESTEROL

It is well established that reducing serum LDL-cholesterol concentration reduces the risk of coronary artery disease [90]. It had been estimated that a 1% reduction in LDL-cholesterol reduces the risk of coronary artery disease by 1.2–2.0% [91]. It is also well-established that a soluble viscous, gel-forming fiber can lower serum total- and LDL-cholesterol, and the degree of cholesterol lowering is highly correlated with the viscosity of the gel-forming fiber: high viscosity is correlated with significant cholesterol lowering; low viscosity is correlated with diminished/no appreciable cholesterol lowering [23]. Clinical studies have shown that the viscosity of a gel-forming fiber is actually a better predictor of cholesterol lowering efficacy than the quantity of fiber consumed [24]. The primary mechanism by which soluble gel-forming fibers lower serum cholesterol is by trapping and eliminating bile. Bile is secreted by the liver (normally 600–1000 mL/day) to emulsify large fat particles into many small particles for digestion by lipase enzymes and absorption across the mucosa [54]. Bile is normally recovered in the distal ileum and recycled, potentially several times within a single meal. When bile is trapped in a gel-forming fiber and eliminated via stool, the liver must produce more bile to meet digestive needs. Cholesterol is a component of bile, and the liver uses serum stores of cholesterol to generate more bile, effectively lowering serum LDL-cholesterol and total-cholesterol, without affecting HDL cholesterol [92].

To assess the importance of viscosity/gel-formation for cholesterol lowering, a clinical study in 26 patients with hypercholesterolemia compared the cholesterol-lowering effects of a medium-viscosity blend of gel-forming fibers (psyllium, pectin, guar gum, and locust bean gum) compared with an equal amount of low-viscosity gum Arabic (Acacia gum, highly branched) [93]. The fibers were consumed in a beverage three times daily (5 g/serving) for 4 weeks. Diet, exercise, and body weight were held constant. The medium-viscosity gel-forming blend exhibited a 10% reduction in total cholesterol ($p < 0.01$) and a 14% reduction in LDL-cholesterol ($p < 0.001$), with no significant change in HDL or triglycerides. In contrast, the low-viscosity gum Arabic-treated group showed no change in any plasma lipid characteristics [93]. A second publication with 4 studies (duration 4–12 weeks) explored the plasma lipid-lowering effects of a variety of soluble dietary fibers [94]. The studies were randomized, double-blind, placebo-controlled trials involving men and women with hyperlipidemia (plasma cholesterol >200 mg/dL). Low viscosity gum Arabic (acacia gum) consumed for 4 weeks as the sole fiber source (15 g/day) or the primary fiber source in a soluble fiber blend (17 g/day; 56% acacia gum) did not produce a significant lipid-lowering effect versus placebo. In contrast, 15 g/day of a medium-viscosity blend of soluble fibers (psyllium, pectin, guar gum, and locust bean gum) consumed for 4 weeks yielded significant reductions in total cholesterol (8.3%) and LDL-cholesterol (12.4%)($p < 0.001$) that were comparable to 10 g/day high-viscosity raw guar gum. Note that the lipid-lowering benefit of the medium viscosity blend of soluble fibers (psyllium, pectin, guar gum, and locust bean gum) showed a dose-response effect for reducing LDL-cholesterol: placebo +0.8%; 5 g/day—5.6%; 10 g/day—6.8%, and 15 g/day—14.9% (all doses $p < 0.01$ versus placebo). The effects of the soluble viscous/gel-forming fibers on plasma lipids were similar in both men and women. The authors concluded that the findings support the usefulness of soluble viscous/gel-forming fibers as a cholesterol lowering therapy, but cautioned against ascribing cholesterol lowering benefits solely on a classification of solubility [94]. As with improved glycemic control, viscosity/gel-formation is a key driver of efficacy for lowering cholesterol in patients with hyperlipidemia.

Low viscosity fiber supplements (gum Arabic/acacia gum), non-viscous fiber supplements (e.g., inulin, wheat dextrin) and viscous non-gel forming fiber supplements (e.g., methylcellulose) will not exhibit a significant cholesterol-lowering benefit [23,66,93–95]. In contrast, viscous, gel-forming fiber supplements (e.g., psyllium, pectin, guar gum, locust bean gum) will exhibit a significant cholesterol lowering benefit if the final processing of the marketed product has not significantly altered the viscosity/gelling capacity of the raw fiber [4,5,23,24,66,73,76–78,96–98]. For example, two clinical studies investigated the effects of β-glucan from oat bran, either baked into bread and cookies (study 1), or provided as a raw fiber in orange juice (study 2), on serum cholesterol in 48 subjects with hypercholesterolemia [87].

In study 1, subjects completed a 3-week baseline with control bread and cookies rich in wheat fiber (insoluble, no effect on cholesterol) followed by a 4-week treatment period where they were randomly assignment to remain on the control fiber products (placebo), or switch to bread and cookies enriched with β-glucan (5.9 g/day). The β-glucan baked into bread and cookies had no effect on serum LDL-cholesterol as compared to the control fiber. In contrast, study 2 provided a lower dose of β-glucan (5 g/day) in orange juice, which significantly decreased LDL-cholesterol versus the wheat fiber control ($p < 0.001$). The authors concluded that food matrix, food processing, or both, could adversely affect the cholesterol-lowering efficacy of β-glucan [87]. This emphasizes the importance of recognizing that not all marketed fiber supplements will provide the clinical efficacy of the original raw fiber.

As mentioned above for glycemic control, it is not only important to recognize the specific fiber in a supplement to understand its potential health benefits, but also the degree and type of processing the raw fiber has been exposed to in preparing the marketed product. As discussed previously, the cholesterol-lowering effectiveness of β-glucan depends on its ability to retain its gelling nature, significantly increase the viscosity of chyme, and trap/eliminate bile. The viscosity/gelling nature of β-glucan, in turn, is determined by its molecular weight (chain length), which can be influenced by methods of processing and storage of the final fiber product [23]. High and medium molecular weight cereals significantly lowered serum LDL-cholesterol (high viscosity > medium viscosity) versus wheat bran, while low molecular weight β-glucan (low viscosity) failed to show a significant difference versus wheat bran. Also remember that within a given viscous/gel-forming fiber (e.g., β-glucan), molecular weight correlates with viscosity. It is across fiber comparisons of molecular weight that may *not* be predictive of viscosity (straight chain versus highly branched). Considered together, these studies support that the cholesterol lowering benefit of fiber supplements is proportional to the viscosity of gel-forming fibers. The higher the viscosity of a marketed gel-forming fiber supplement product when hydrated, the greater the potential cholesterol lowering benefit. Again, the simple test referred to previously can be conducted to predict the potential cholesterol-lowering benefit of a fiber supplement.

As with glycemic control, the potential for a cholesterol lowering benefit is also highly influenced by the baseline cholesterol level: soluble viscous, gel-forming fibers have no appreciable effect on cholesterol concentrations in healthy subjects with normal cholesterol concentrations, but exhibit a progressively greater benefit as baseline cholesterol exceeds normal concentrations. Also, as observed with improved glycemic control, the cholesterol-lowering benefit of soluble viscous, gel-forming fiber supplements is observed in addition to the benefits conveyed by the prescription drugs in patients already being treated for hyperlipidemia. Eight clinical studies have shown that psyllium (gel-forming fiber) enhanced the cholesterol lowering benefit of prescription drugs when dosed as a co-therapy to statin drugs (class of drugs used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase) or bile sequestrants (bind bile in the gastrointestinal tract to prevent its re-absorption) [96–104]. Also, as with improved glycemic control, a soluble viscous gel-forming fiber supplement can lower the required dose of a prescription statin drug. In a 12-week randomized, double-blind study including 68 patients with hyperlipidemia, a low dose of simvastatin (10 mg) combined with psyllium (15 g/day) was superior to the low dose of simvastatin alone (−63 mg/dL versus −55 mg/dL, respectively; $p = 0.03$), and identical to a high dose of simvastatin (20 mg, −63 mg/dL) for lowering elevated serum LDL-cholesterol concentration [99].

8.5.2 SMALL INTESTINE: EFFECTIVENESS OF FIBER SUPPLEMENTS ON SATIETY AND WEIGHT LOSS

The Center for Disease Control has declared obesity an epidemic in the United States [105]. More than one-third of United States adults (35.7%) are obese, and obesity-related conditions include heart disease, stroke, type 2 diabetes, and certain types of cancer [105]. The estimated annual medical cost of obesity in the U.S. was $147 billion in 2008 [105]. Observational studies have shown an inverse association between body weight and high intakes of dietary fiber (e.g., replacement), and a high-level of dietary fiber consumption can reduce the risk for gaining weight or developing obesity by approximately 30% [106–108]. Early clinical studies dosed fiber supplements to facilitate weight loss [109,110]. Epidemiologic studies show that diets high in fiber and whole grains are associated with lower body weight, and prevention of weight gain, compared to diets low in fiber and whole grains [111,112]. As discussed in previous sections, however, care must be taken when attributing health benefits to "fiber supplements" in general, as they reflect a heterogeneous group of fibers sources that differ in their physicochemical properties, and ability to affect appetite and energy intake [113–116]. It is also important to understand the terminology, for while "satiation" and "satiety" are often used interchangeably, their actual meaning is different. Satiation is your reaction during a meal that causes you to stop eating a given meal. Satiety is the response to availability of nutrients from food consumed, that is being/has been digested. So claims relative to "feel full longer" and "helps you feel less hungry between meals" are related to satiety. A recent comprehensive review of available clinical data concluded that resistant starch (soluble, non-viscous, fermentable) (e.g., wheat dextrin) had no significant effect on satiety or weight loss at physiologic doses [117]. A year-long study in 97 adolescents has been quoted as demonstrating weight loss for a "prebiotic" fiber supplement (soluble, non-viscous, fermentable), but a closer look at the data shows that the prebiotic fiber group (8 g/day) was not different from baseline for body mass index (BMI) [118]. The study appeared to show a favorable result because there was a significant increase in BMI in the control group (fed maltodextrin, readily digested/absorbed as glucose), so at best an argument could be made that the prebiotic fiber was a healthier option than the maltodextrin substitute, but the data do not support a claim for weight loss [118].

In contrast to non-viscous, fermentable fiber supplements (e.g., inulin, wheat dextrin), soluble viscous, gel-forming fibers, such as guar gum, pectin, and psyllium, have been shown to increase satiety and reduce subsequent energy intake [119–121]. A well-cited experiment on fiber-induced satiety demonstrated that apples were significantly more satiating than fiber-free apple juice, even though the juice provided the same level of carbohydrate as the apples [122]. Pectin, the soluble viscous, gel-forming fiber present in apples, has been shown to delay gastric emptying and increase satiety [123]. Soluble, viscous, gel-forming fibers can influence satiety by several mechanisms mentioned previously, including delayed degradation and absorption of nutrients in the small bowel, leading to a "sustained" delivery of nutrients, and delivery of nutrients to the distal ileum with subsequent stimulation of feedback mechanism like the "ileal brake" phenomenon and decreased appetite [4,5,114–116]. Some studies of the effects of gel-forming fiber on satiety used either an insoluble fiber or a soluble non-viscous fiber as a negative control, supporting the assertion that the effect on satiety for fiber supplements is proportional to viscosity/gel-formation [21,23–25,119,124]. Satiety often is assessed in short-term clinical studies as a tool or mechanism for predicting the potential for weight-loss effects, but the end therapeutic goal is weight loss (or prevention of weight re-gain). Showing a long-term (e.g., 6-months or longer) reduction in body weight in a clinical study, however, can be much more challenging than a short-term difference in satiety. A review of the effects of fiber supplements on weight loss [125] identified 17 placebo-controlled clinical studies. In most studies, subjects were maintained on energy-restricted diets, and fiber supplements (mostly insoluble fiber) were provided three times daily before meals. Fiber supplement intake ranged from 4.5 to 20 g/day. Results show that only 1 of 17 studies provided evidence of weight loss greater than placebo [125].

One factor that may not have been considered in previous weight loss studies is the degree of fermentation of the fiber supplements tested. Fermentation of a fiber supplement releases nutrients into the gut that are absorbed into the blood stream, so fermentable fibers are not calorie free. A 6-month study compared objective measures of health benefits for a viscous, gel-forming, non-fermented fiber (psyllium) versus a less viscous, readily fermented fiber (PHGG) [76]. This randomized, controlled, 6-month study included 141 patients with metabolic syndrome maintained on a restricted diet alone (negative control) or the restricted diet supplemented with psyllium or PHGG (both dosed 3.5 g twice a day with breakfast and dinner). The control group (restricted diet alone) showed a gradual loss in weight over the first 4 months, followed by a gradual weight re-gain. After 2 months, the guar gum treatment group showed a marked weight reduction (−2.4 kg versus baseline), but this reversed to weight re-gain over the following 4 months (Figure 8.8). In contrast, the psyllium treatment group showed gradual and continued weight loss across the 6-month test period. At 6 months, weight loss for the psyllium treatment group was −3.3 kg versus baseline, −2.1 kg versus placebo, and −1.76 kg versus guar gum ($p < 0.01$ for all 3 comparisons; Figure 8.8) [76]. The data suggest that two fiber characteristics, high viscosity/gel-forming, and non-fermented, played key roles in the greater long-term weight loss observed in the psyllium treatment group. This study also emphasizes the importance of longer-term studies. The conclusions drawn from this study would be quite different had it stopped at 2 or 4 months, potentially affecting the clinical advice offered to patients/clients, and their future success in weight loss/maintenance programs [76].

8.5.3 SMALL INTESTINES: EFFECTIVENESS OF FIBER SUPPLEMENTS IN METABOLIC SYNDROME

According to the International Diabetes Federation, Metabolic Syndrome is defined as a cluster of the most dangerous heart attack risk factors: diabetes and raised

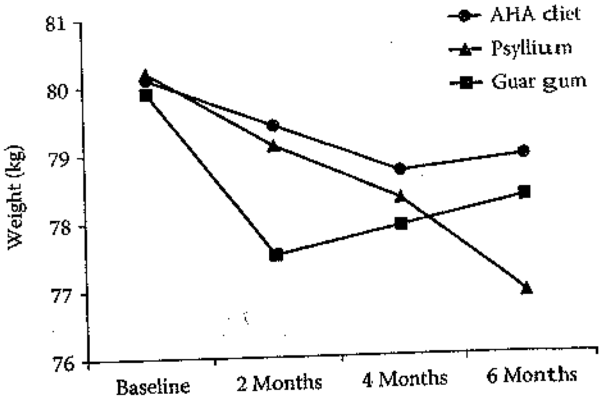

FIGURE 8.8 Both viscosity and fermentation affect fiber supplement-related weight loss efficacy. In a 6-month study in patients with Metabolic Syndrome, a restricted diet alone showed a modest weight loss over 4 months, followed by weight re-gain. In addition to the restricted diet, psyllium (3.5 g twice a day), a viscous, gel-forming, non-fermented fiber supplement, showed sustained weight loss over a 6-month study [76]. In contrast, PHGG, a less viscous readily fermented fiber at the same dose and restricted diet, showed a marked weight loss followed by weight re-gain. The data support that clinical studies assessing weight loss should be at least 6 months in length. The data further support that psyllium (viscous, gel-forming, not fermented), in conjunction with a healthy diet, is more effective for long-term weight loss than a healthy diet alone, or a healthy diet with a less viscous, fermented fiber (PHGG). (Figure recreated with permission from McRorie J, Fahey G. 2013. *Clin Nurs Stud.* 1(4), 82–92.)

fasting plasma glucose, abdominal obesity, high cholesterol, and high blood pressure [126]. The Federation also states that people with metabolic syndrome are twice as likely to die from, and three times as likely to have, a heart attack or stroke compared with patients without the syndrome, and have a five-fold greater risk of developing type 2 diabetes [126]. It was estimated that 1/4 of adults worldwide have Metabolic Syndrome [126]. Given the growing evidence that soluble viscous, gel-forming fiber supplementation improves indices related to insulin resistance [78,81,127,128], cholesterol lowering, improved glycemic control and weight loss, all risks associated with metabolic syndrome, it is reasonable to predict that viscous gel-forming fibers will also show efficacy in attenuating objective clinical measures of Metabolic Syndrome. In the same 6-month study mentioned above, the investigators assessed the clinical benefits of two soluble viscous fibers in 141 patients with metabolic syndrome [76]. Patients were fed an American Heart Association step-2 diet alone (control), or the same diet supplemented with psyllium or guar gum (both dosed at 3.5 g twice a day with breakfast and dinner). After 6 months of treatment both psyllium and guar gum treatment groups showed significant improvement in BMI (−7.2% versus −6.5%), fasting plasma glucose (−27.9% versus −11.1%), fasting plasma insulin (−20.4% versus −10.8%), HbA1c (−10.4% versus −10.3%), and LDL cholesterol (−7.9% versus −8.5%), respectively [76]. Only the psyllium group exhibited a significant improvement in plasma triglyceride concentration (−13.3%) and systolic (−3.9%) and diastolic (−2.6%) blood pressure. At the conclusion of the study, 12.5% of patients in the psyllium group no longer qualified for a diagnosis of Metabolic Syndrome, versus 2.1% of patients in the guar gum group and 0% of patients in the diet-alone group [76]. Considered together, these data support that a soluble viscous, gel-forming fiber supplement can be an effective co-therapy for treating Metabolic Syndrome.

8.6 PHYSICAL EFFECTS OF FIBER SUPPLEMENTS IN THE LARGE INTESTINE

The large intestine is comprised of the cecum (most proximal portion, receives liquid residue from ileum), the colon (ascending, transverse, descending, and sigmoid), the rectum, and the anus. The large bowel exhibits a series of chambers known as "haustrations" (Figure 8.9), and a triangular appearance due to the three strips of longitudinal muscle known as "taenia coli" (Figure 8.9) [5,54]. Approximately 1500 mL of liquid residue arrives in the large intestine daily. Normally, over 90% of the water and electrolytes that arrive in the cecum are absorbed by the large intestine, eventually resulting in formed stool. The motor events of the large intestine are approximately 95% segmental ("mixing" waves) that facilitate the absorption of water and electrolytes, while the remaining approximately 5% are propagating contractions (peristalsis) [129]. Propagating contractions in the large bowel occur across a wide range of amplitudes and propagating rates, where amplitude is inversely proportional to propagation rate (high amplitude = slowly propagating; low amplitude = rapidly propagating) [129]. The rate of propagation is also proportional to

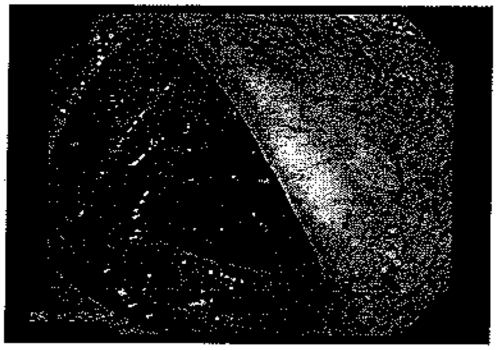

FIGURE 8.9 Endoscopic view of the large intestine. This is an endoscopic view of the large intestine. As opposed to the millions of villi that stud the mucosa of the small intestine (Figure 8.5), the mucosa in the large intestine is relatively smooth (no villi, smaller surface area), but still highly vascular. Note the segmented appearance (haustra) of the large bowel, and the triangular appearance of each chamber resulting from the three strips of longitudinal muscle (taenia coli) on the surface of the large bowel. (Reprinted with permission from Julio Murra-Saca, Chief of Department of Gastroenterology, Hospital Centro de Emergencias; El Salvador Atlas of Gastrointestinal Video Endoscopy.)

the frequency of the specific wave types (slowly propagating = few per day; rapidly propagating = many per day) [129]. The two proportionalities provide a wide range of propagating contractions. At one extreme, high amplitude (>100 mm Hg), slowly propagating (≤1 cm/s) contractions are infrequent (≤6/day) lumen-occluding events that propel all large bowel contents (gas, liquids, soft to hard stool) toward the anus. At the other extreme, low amplitude (10 mm Hg), rapidly propagating (≥10 cm/s) contractions are frequent events (≥30/day) that act like a "squeegee" to propel gas more rapidly than all other gut contents. There are also "medium amplitude/propagating rate" contractions that populate the middle of the range, between extremes [5,54,129–132].

When considered in light of the different viscosities present in the large bowel (e.g., gas, liquid/loose/soft/formed/hard stool), the rate of transit through the large intestine is a function of the frequency and amplitude/rate of propagating contractions versus the viscosity of the substrate [129]. For example, gas is propelled by all propagating contractions, from infrequent high amplitude slowly propagating contractions (HAPCs) that are lumen-occluding events that propel all contents, to frequent low amplitude, rapidly propagating contractions that propel only gas, making gas the most rapidly propelled substrate in the gut. Gas can transit the entire gastrointestinal tract in less than 1 h (flatulence approximately 14 episodes/day) [5,129]. Liquid stool is propelled by all but the smallest/fastest propagating contractions that propel only gas, resulting in rapid transit through the large bowel (e.g., diarrhea) and the potential for multiple bowel movements a day [5]. In contrast, formed or hard stool is only propelled by infrequent HAPCs, and transit through the chambered large bowel can require days (approximately one bowel movement/day) [5]. This is why fiber that retains its gel-forming nature and exerts a significant stool softening (water-holding) effect can result in faster transit and more frequent bowel movements, which can provide clinical relief from constipation.

8.6.1 LARGE BOWEL EFFECTS: FIBER BENEFITS IN PATIENTS WITH CONSTIPATION AND DIARRHEA

The laxative effects of fiber can be driven by several different physicochemical properties of fiber. Despite the lack of water-holding capacity, insoluble fiber (e.g., wheat bran) can increase fecal mass and colonic transit rate by mechanical stimulation (irritation) of gut mucosa, inducing secretion and peristalsis [4,5,67,130]. The importance of this effect was illustrated in an early study comparing the laxative efficacy of wheat bran, ground to varying particle sizes, with that of inert plastic particles, cut in size to match the different wheat bran particles. Note that plastic particles are not fermented and have no water-holding capacity [133]. The laxative effect of the wheat bran was comparable to that of the plastic particles: a greater laxative effect was associated with larger particles, while no laxative effect was observed with fine particles. A subsequent investigation confirmed that the stimulatory effect of particles in the intestinal lumen depends on both particle size and shape, with large coarse (gritty) particles having a greater laxative benefit than fine, smooth particles [134]. Thus, insoluble fiber can provide a laxative benefit, but only if the fiber supplement provides large, coarse particles. Highly processed, finely ground insoluble fiber (e.g., whole wheat flour) will not provide a significant laxative benefit. Further, with no water-holding capacity and no gel-forming capacity, insoluble fiber supplements cannot be of benefit for attenuating loose/liquid stools in diarrhea. The mucosal stimulating/irritating effect of insoluble particles could actually make symptoms of diarrhea worse [135].

Soluble non-viscous, readily fermented fiber supplements (e.g., wheat dextrin, inulin) dissolve in water with no appreciable change to viscosity, and are readily fermented in the large bowel, resulting in dose-dependent gas production and an increase in flatulence, but without a significant laxative benefit at physiologic doses [4,5,136–138]. Similarly, viscous soluble fibers that are readily fermented (e.g., β-glucan, guar gum) will also result in a dose-dependent increase in gas formation, leading to a potential increase in flatulence, but fermentation of the fiber results in loss of viscosity and water-holding capacity, resulting in a no appreciable laxative benefit at physiological doses [37,40,60].

There are few studies on the effects of readily fermented fibers on diarrhea in adults. A study of antibiotic-induced diarrhea had patients consume oligofructose (12 g/day) while taking a broad-spectrum antibiotic for 7 days, followed by another 7 days of the prebiotic therapy (after stopping the antibiotic therapy) [139]. The study showed that the readily fermented fiber was not different from placebo for the incidence of diarrhea, *Clostridium difficile* infections, or hospital stays. Another study assessed the risk of developing traveler's diarrhea, and reported that consumption of fructooligosaccharides (10 g/day) for a 2-week pre-travel period, and continued during the 2-week travel period to destinations of medium and high risk, had no effect on the prevention of traveler's diarrhea [140]. Another study of traveler's diarrhea was a placebo-controlled, randomized, double blind of parallel design in 159 healthy volunteers who traveled for minimum of 2 weeks to a country of low or high risk for travelers diarrhea [141]. In this study, a novel galactooligosaccharide (GOS; 5.5 g/day) was compared to placebo (maltodextrin), and the results showed significant improvement with GOS versus control for the incidence ($p < 0.05$) and duration ($p < 0.05$) of travelers diarrhea. While prebiotics remain an area of emerging science, and there is a rationale for the use of soluble, non-viscous, readily fermented fibers in the prevention of infectious diseases, the totality of clinical data for currently marketed non-viscous, readily fermented fiber supplements is mixed at best, and does not readily support a clinically meaningful benefit in attenuating symptoms of constipation or diarrhea at physiologic doses.

For a fiber supplement to be beneficial in attenuating both constipation and diarrhea, it should have high water-holding capacity, and retain its gelled, visco-elastic nature throughout the large bowel. In other words, it should be a gel-forming fiber that is not fermented. Most soluble viscous, gel-forming fiber supplements (e.g., guar gum, Acacia gum, β-glucan from oats and barley) are readily fermented in the large bowel, resulting in a loss of their gelled nature, leading to no significant benefit for improving symptoms of constipation or diarrhea [4,5,60]. In contrast to the other fiber supplements discussed above (poorly fermented insoluble fiber, readily fermented soluble non-viscous fibers, and readily fermented soluble viscous fibers), a fourth fiber category exists that is soluble, viscous, gel-forming, and non-fermented. This fiber category (i.e., psyllium) maintains its gelled state/

water-holding capacity throughout the large bowel [67]. Consumption of a gel-forming, non-fermented fiber with high water-holding capacity results in a dose-related formation of high moisture, soft, bulky stools [67,142–144], without an increase in gas production or flatulence [37–41]. Further, a fiber that retains its gel/water-holding capacity throughout the large bowel provides a dichotomous, "stool normalizing" effect: it decreases the viscosity of hard stool in constipation (softer stool, increased transit rate, improved bowel movement frequency) [144], and improves the viscosity of loose/liquid stool in diarrhea (firmer stool, slower transit rate, less frequent bowel movements) [145–147]. Stool consistency is highly correlated with stool water content, and a relatively small change in stool water content (e.g., an increase of 5% water content) can lead to a relatively large stool softening effect (five-fold difference in stool viscosity) [67]. In a randomized, double-blind, clinical study, 170 patients with chronic idiopathic constipation underwent 2 weeks of therapy with either a gel-forming, non-fermented fiber (psyllium, 5.1 g twice daily) or a marketed stool softener, docusate sodium (100 mg twice daily) [144]. Results show that psyllium was superior to docusate for increasing stool water content ($p = 0.007$) and the frequency of bowel movements ($p = 0.02$) [144]. The stool softening effect of psyllium gradually increased over the treatment period, suggesting that the stool softening benefit would not be lost with long-term daily dosing. The American College of Gastroenterology Chronic Constipation Task Force systematically reviewed the available clinical evidence regarding the use of fiber supplements in chronic constipation, and concluded that there was insufficient clinical evidence to support a recommendation for calcium polycarbophil, methylcellulose, or bran, but concluded that psyllium was the only fiber supplement with sufficient clinical evidence to support a recommendation for treatment of chronic constipation (Grade B recommendation) [148]. Clinical studies have also documented the beneficial effects of psyllium in attenuating symptoms in diarrhea, including reducing the frequency of bowel movements and improving stool form in chronic diarrhea [147,149], lactulose-induced diarrhea [150], Crohn's disease [151], and phenolphthalein-induced diarrhea [146]. Taken together, the clinical data support that two fiber supplements can provide a significant health benefit for constipation (e.g., insoluble bran of sufficient coarseness, and psyllium), where as only one fiber supplement (psyllium) has been shown to act as a stool normalizer, softening hard stool in constipation and firming loose/liquid stool in diarrhea [5].

8.6.2 LARGE BOWEL EFFECTS: FIBER BENEFITS IN PATIENTS WITH IRRITABLE BOWEL SYNDROME

Another potential area of benefit for fiber supplements is a functional bowel disorder known as IBS. IBS is manifested by chronic, recurring abdominal discomfort/pain often associated with disturbed bowel habit, but in the absence of structural abnormalities that would account for the symptoms [152]. In addition to abdominal discomfort/pain, typical symptoms can include sensations of distension, cramping, bloating, flatulence, and changes in stool form and frequency. The use of dietary fiber is frequently recommended to normalize bowel function and reduce pain in patients with IBS, but, as discussed above, not all fiber supplements are equal in clinically-demonstrated efficacy [153–155]. A randomized 12-week clinical study in a primary care setting included 275 patients (aged 18–65 years) with IBS, and assessed the effectiveness of a soluble fiber supplement (psyllium 10 g), an insoluble fiber supplement (wheat bran 10 g), or placebo (rice flour) in two daily doses taken with meals [154]. The primary end point was adequate symptom relief, analyzed after 1, 2, and 3 months of treatment to assess both short-term and sustained effectiveness. Results showed that the proportion of responders was significantly greater in the psyllium group than in the placebo group, and bran was not different from placebo. After three months of treatment, symptom severity in the psyllium group was reduced by 90 points, compared with 49 points in the placebo group ($p = 0.03$). Again, the bran group was not different from placebo. The authors concluded that "psyllium offers benefits in patients with IBS in primary care" [154]. A recent (2013) comprehensive review on the effects of fiber in functional bowel disorders assessed a wide range of products, including oligosaccharides, pectin, guar gum, oats, inulin, psyllium, wheat bran, flax seed, cellulose, and methylcellulose [155]. The authors determined that knowing the relative degree to which a fiber is fermented is of clinical importance when making a recommendation [155]. The byproducts of fermentation can affect gastrointestinal function and sensation, and rapid gas production can lead to increased flatulence and other gastrointestinal symptoms. The authors concluded that a recommendation for psyllium was best supported by the available clinical evidence [155], and a subsequent published letter to the editor [156] further clarified the clinical data supporting that psyllium is not fermented in the gut. An earlier systematic review, conducted by the American College of Gastroenterology Task Force on IBS, also concluded that psyllium was effective for IBS, and assigned it a conditional recommendation [153].

In contrast, in a meta-analysis of five studies that compared insoluble bran with either a low fiber diet or placebo, bran failed to improve overall IBS symptoms [157]. Insoluble fibers, including wheat bran and corn bran, are not recommended for routine use in patients with IBS. Not only have these insoluble fibers not demonstrated efficacy over placebo in this setting, some studies also suggest that bran, with its mechanical stimulation/irritation of the gut mucosa, may worsen IBS symptoms [135,158]. A few studies have assessed the efficacy of soluble non-viscous, readily fermented fibers in adult patients with IBS. One study [159] assessed the effects of a 20 g dose of a readily fermented fructooligosaccharide, and found that after 4–6 weeks on treatment, IBS symptoms became markedly worse versus placebo. With continued dosing (out to 12 weeks), an apparent adaptation occurred, and symptoms returned to a level not significantly different from placebo. A reasonable conclusion is that large doses of any fermentable fiber should not be recommended to patients with IBS. A second study found that a more modest dose (6 g/day) of oligofructose had no effect on IBS symptoms [160]. A third study again assessed a relatively modest dose of fermentable short chain fructooligosaccharides (5 g/day for 6 week) in patients with IBS symptoms, and showed a statistically significant improvement in symptoms versus placebo, but less than half of the 105 randomized subjects were included in the per-protocol analysis, and no intent-to-treat analysis was provided for efficacy [161]. A fourth study assessed the effects of 6 weeks of treatment with a trans-galactooligosaccharide at two dose levels (3.5 or 7 g/day) versus placebo, and found that the lowest dose significantly improved bloating, flatulence, and abdominal pain, while the 7 g dose did not improve any of these three symptoms of IBS [162]. Considered together, these data support that insoluble fiber supplements (e.g., wheat bran, corn bran) and fermentable fiber supplements (e.g., inulin, wheat dextrin, polydextrose, Acacia, maltodextrin, guar gum) should not be recommended for patients with IBS. A gel-forming, non-fermentable fiber supplement (i.e. psyllium) that acts as a stool normalizer (softens hard stool in constipation, firms loose/liquid stool in diarrhea) is well-suited for patients with IBS, and was recommended in both a recent review in the *American Journal of Gastroenterology* [155], and by the American College of Gastroenterology Task Force on IBS [153].

8.7 WHY FIBER SUPPLEMENTS CAN CAUSE GASTROINTESTINAL SYMPTOMS, AND HOW TO AVOID SYMPTOMS TO FACILITATE LONG-TERM COMPLIANCE

8.7.1 Discomfort and Cramping Pain

Sensations of slight discomfort to cramping pain may be associated with an increase in consumption of dietary fiber, particularly if the patient is constipated and a fiber supplement is initiated at a relatively high dose [4,5]. Lower intestinal symptoms can be replicated by passive stretch of the bowel wall via stepwise inflation of a balloon in the colon and rectum, generating sensations ranging from vague awareness to severe cramping pain with increasing intra-luminal pressure [163–165]. This suggests that the term "cramping pain" is actually a misnomer, as the term "cramping" implies spastic bowel wall contraction. Sensations including slight discomfort, the urge to defecate, and cramping pain, are also strongly correlated with HAPCs [4,5,163,165], suggesting that physiologic colonic motor events give rise to these sensations. Studies conducted with healthy subjects demonstrated that sensations of cramping pain were associated with the passage of formed stool followed by loose/liquid stool, objectively characterized as a high "stool viscosity ratio" (highest viscosity stool value divided by the lowest viscosity stool value in a given day) [166]. In the large bowel, HAPCs (peristalsis) have been correlated with mass movements, propelling luminal contents toward the rectum [32,166,167].

8.7.2 Stool Form and Cramping Pain—A Collision of Divergent Viscosities

When stool is formed, and of similar consistency (Figure 8.10), it resists significant deformation, so the forces associated with the propelled stool remain axial, and no significant bowel wall distention is generated. In normal individuals, this propulsion is not typically perceived unless it causes stool to fill the rectum, stimulating an urge to defecate [4,5,166]. In contrast, if a propagating contraction causes a bolus of lower-viscosity stool to collide with more distal formed stool (Figure 8.11), acute dilation of the bowel wall can occur, stretching mechanoreceptors, and causing sensations from discomfort to cramping pain. The discomfort/pain would be transient,

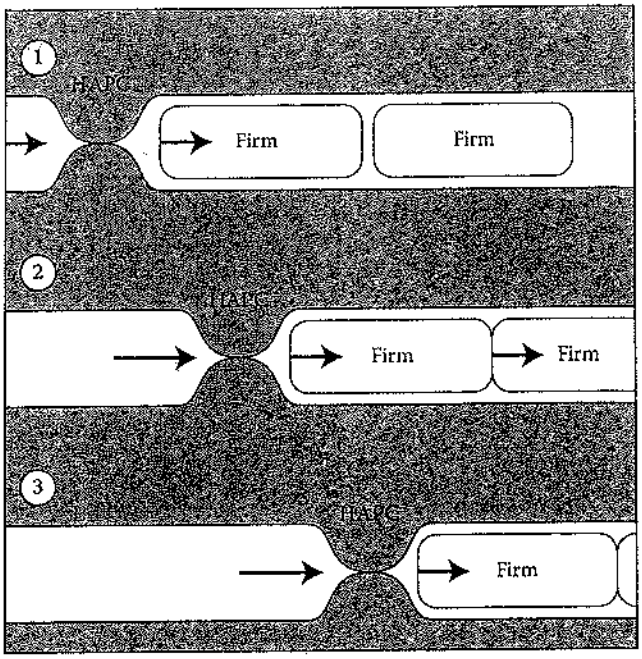

FIGURE 8.10 Stool of similar (firm) consistency does not stress the bowel wall. A model for the transit of firm digesta/stool [167]. Frame 1, high-amplitude propagating contraction (HAPC) propels stool toward the rectum. Frames 2 and 3, an HAPC propels formed stool against more distal formed stool. Both segments of stool are of sufficient viscosity to resist deformation, so the forces remain axial and no significant bowel wall distension is generated. In normal individuals, this propulsion would not be perceived until the stool filled the rectum, stimulating an urge to defecate. (Reprinted with permission from Chutkan R et al. 2012. *J Am Acad Nurse Pract.* 24, 476–487.)

occurring with the frequency of propagating contractions and relieved with a bowel movement. Such a bowel movement would consist of formed stool followed by loose/liquid stool. Given the importance of minimizing GI symptoms to improve adherence with a new fiber therapy, taking steps to keep the stool viscosity ratio low is an important consideration. For non-constipated subjects, this entails starting a new fiber supplement gradually, initiating dosing at no more than 3 or 4 g/day the first week, then increasing by one daily dose each subsequent week until 3–4 doses of the supplement per day is achieved (about 10–15 g/day). For constipated patients, any introduction of a new fiber regimen carries a significant risk of cramping pain unless the hard stool present in the distal large bowel is eliminated before initiation of a fiber supplement. A reasonable suggestion is to first clear the hard stool from the bowel with a significant dose of an osmotic laxative (e.g., polyethylene glycol). The ensuing cramping pain and potential loose stool following evacuation of the hard stool will be associated with the osmotic laxative, not a fiber supplement. Once the hard stool is cleared, gradually introduce a new fiber supplement as above. This may improve long-term compliance with a new fiber supplement.

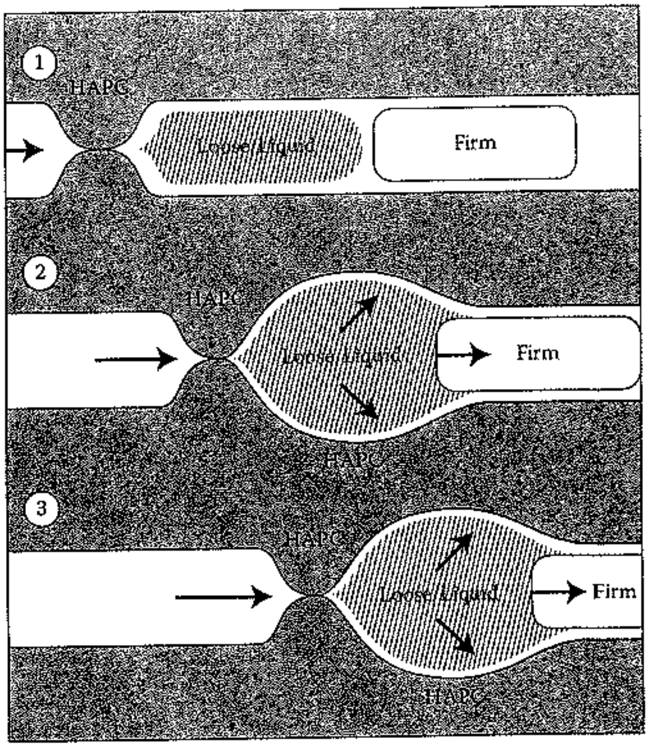

FIGURE 8.11 Acute bowel wall distention with disparate stool viscosities. A model for the transit of low-viscosity digesta [167]. Frame 1, an HAPC propels soft stool toward the rectum. Frames 2 and 3, an HAPC propels soft stool against more distal firm stool. The soft stool is readily deformable, and the forces are no longer axial but extend radially (oblique arrows), causing acute GI symptoms. The symptoms (e.g., cramping pain) would be intermittent with the frequency of HAPCs and relieved by a bowel movement. (Reprinted with permission from Chutkan R et al. 2012. *J Am Acad Nurse Pract.* 24, 476–487.)

8.8 CONCLUSIONS

Despite the general consensus that fiber is "good for you," each specific health benefit attributed to dietary fiber is associated with specific fiber characteristics, so it is important to have a good understanding of the fiber characteristics that provide each health benefit (Table 8.1). Insoluble fiber (e.g., wheat bran) has been shown to have a laxative benefit by mechanical stimulation/irritation of the intestinal mucosa, but only if the fiber particles are of sufficient "grittiness." Soluble non-viscous fiber supplements (e.g., inulin, wheat dextrin, polydextrose, maltodextrin) are readily fermented, and whereas these fibers are part of an emerging science (e.g., prebiotics) with a plethora of data showing significant and potentially beneficial effects on the gut microbiome, there is only limited reproducible, well-controlled clinical data demonstrating a clinically meaningful health benefit at physiologic doses for these marketed fiber supplements. In contrast, there are numerous well-controlled clinical

TABLE 8.1
Clinically Demonstrated Health Benefits Associated with Common Fiber Supplements

	No Water-Holding Capacity			Water-Holding Capacity			
	Insoluble	**Soluble, Non-Viscous**		**Soluble Viscous**	**Soluble Gel-Forming**		
	Wheat Bran	**Wheat Dextrin**	**Inulin**	**Methylcellulose**	**Partially Hydrolyzed Guar Gum**	**β-glucan**	**Psyllium**
Source	Wheat	Chemically treated wheat	Chicory root	Chemically treated wood pulp	Guar Beans	Oats, Barley	Seed husk, Plantago ovata
Degree of fermentation	Poorly fermented	Readily fermented	Readily fermented	Non-fermented	Readily fermented	Readily fermented	Non-fermented
Cholesterol lowering					+/–[b]	+[c]	+
Improved glycemic control					+/–[b]	+[c]	+
Satiety						+[c]	+
Weight loss							+
Constipation/Stool softener	+[a]			+/–[d]			+
Diarrhea/Stool normalizer							+
Irritable bowel syndrome (IBS)							+

[a] If particle size is sufficiently large/coarse.

[b] The efficacy of PHGG depends on the degree to which it has been hydrolyzed. If a marketed product has little/no viscosity when mixed with water (as described above), then it will not exhibit significant gel-dependent health benefits.

[c] Typically marketed in fiber bars or cereals, requiring pressure and/or heat to make the final product, potentially reducing gel-forming capacity.

[d] Methylcellulose has an OTC indication for treatment of occasional constipation, but the American College of Gastroenterology determined that methylcellulose had insufficient clinical data to recommend it for treatment of chronic constipation.

studies demonstrating viscosity/gel-dependent health benefits associated with small bowel function, including cholesterol lowering and improved glycemic control. The greater the viscosity/gel-forming capacity exhibited by a soluble fiber, the greater the potential health benefit. Highly viscous, gel-forming fiber supplements (e.g., high molecular weight β-glucan, raw guar gum, psyllium) have been shown clinically to lower serum LDL-cholesterol concentrations in patients with hyperlipidemia, and improve glycemic control in patients with Type 2 Diabetes and Metabolic Syndrome. Both the cholesterol lowering and improved glycemic control benefits are observed in addition to the effects already conveyed by prescription drugs to treat hyperlipidemia and hyperglycemia, demonstrating that viscous/gel-forming fiber supplements can provide an effective co-therapy in patient care. It is important to note that viscosity/gel-dependent health benefits can be lost if a marketed fiber supplement is modified to improve palatability by reducing viscosity (e.g., PHGG), or exposed to extrusion pressure/heat to form the marketed product (e.g., extruded cereal products). A gel-forming fiber supplement can also provide a satiety benefit, as well as a weight loss/weight maintenance benefit, both of which appear dependent on gel-forming capacity and being non-fermented.

For lower gastrointestinal benefits, such as attenuating symptoms in constipation, diarrhea, and IBS, an ideal fiber supplement would be a non-fermented, gel-forming fiber that retains its gelling capacity throughout the large bowel (Table 8.1). Insoluble fiber supplements can be effective for constipation if particles are sufficiently large/coarse, but insoluble fiber supplements should not be recommended for treating diarrhea or IBS due to the mucosa stimulating/irritating mechanism of action that could make symptoms worse. Soluble fiber supplements that are readily fermented, whether non-viscous (e.g., inulin, wheat dextrin, polydextrose, maltodextrin) or viscous (e.g., guar gum, β-glucan), can increase gas/flatulence and bacterial biomass, and provide calories to the host due to fermentation, but have no appreciable laxative effect at physiologic doses. In contrast, a non-fermented fiber that maintains its gel throughout the large bowel (i.e., psyllium) has been shown clinically to meet this definition, acting as a stool normalizer: more effective than the market-leading stool softener for softening hard stool and decreasing symptoms in patients with chronic constipation; effective for firming loose/liquid stools and decreasing symptoms in patients with diarrhea. Psyllium is also the only fiber supplement recommended by the American College of Gastroenterology for treating both chronic constipation and IBS. To decrease the potential for unwanted symptoms associated with starting a new fiber supplement regimen, it is recommended to begin at a relatively low dose, and gradually increase the dose over several weeks. Constipated patients should be encouraged to eliminate hard stools with an osmotic laxative before beginning a new fiber therapy.

Relying on an ingredient name of the raw fiber (e.g., guar gum, oat bran) can be misleading if the marketed supplement no longer provides the same viscosity/gel-forming capacity as the raw fiber. FDA does not require any clinical data on the final marketed product to support a claim for "a good source of fiber". A simple test to predict the potential health benefits of a fiber supplement is to mix a single dose of fiber supplement in a glass of water (usually 2–4 g of fiber; added to 120 mL water), and let it stand for 15 min. If the supplement dissolves in water, then forms a visco-elastic gel, it should provide clinically meaningful, gel-dependent health benefits (e.g., cholesterol lowering, improved glycemic control, satiety/weight loss). If a supplement does not form a gel, it is unlikely to provide these clinically meaningful health benefits. This test is obviously not practical for fiber supplements marketed as fiber bars, yogurts, cereals, or "gummy" dose forms. The vast majority of these products contain a soluble, non-viscous, readily fermented fiber, so the test is not needed, as it has already been established that this category of fiber supplement does not have clinical data supporting health benefits. Note that, for "gummy" fiber supplements, the fiber (e.g., inulin) is non-viscous. The "gum" is a digestible gelatin.

Finally, read the label for the fiber ingredient(s), not the advertising on the marketed product, to determine what fiber source is being provided, and at what dose. Determine if there exists significant clinical evidence to support a health benefit for the raw fiber, and then consider the form of the marketed fiber product, and how processing may have diminished the health benefit(s) of the raw fiber. Be aware that the label claims on a fiber product may not represent the fiber. A product labeled "fiber weight management" may contain one or more fibers that have no supporting clinical data for weight loss or weight maintenance. Several products claim "non-thickening" as a desirable trait, with names implying a health benefit, yet they contain a soluble non-viscous, fermentable fiber with no supporting clinical evidence that the marketed product delivers a health benefit. As discussed above, formulation and processing can affect final product efficacy, so it may not be appropriate to assume that products with the fiber will deliver the same benefits. While one product may have numerous well-controlled clinical studies on the marketed product itself, others with the same active, but a potentially different formulation, may have no clinical support yet make the same health claims. Generic drugs are required to demonstrate bioequivalence and gain regulatory approval before being marketed, but fiber supplements have no similar requirements, so fiber products can make claims without clinical support for their formulation. Not all fiber supplements are equal.

8.8.1 EXAMPLES OF COMMONLY MARKETED FIBER SUPPLEMENTS

Acacia gum (gum Arabic) is a tree exudate collected for centuries by hand from Acacia trees across the Sahelian belt of Africa (North of the equator). The gum oozes from stems and branches of the trees when subjected to stress, including removing sections of bark with an ax. Acacia readily dissolves in water, and the highly branched structure gives rise to a low hydrodynamic volume that yields a low viscosity. A 30% solution of Acacia gum has a lower viscosity than a 1% solution of xanthan gum. Acacia gum is readily fermented by bacteria in the gut, and is part of an emerging area of science related to the microbiome and prebiotics.

Guar gum is a soluble, readily fermented, highly viscous/gel-forming fiber derived from the Indian cluster bean (*Cyanopsis tetragonolopus*). To make the high viscosity gel more palatable as a dietary supplement, raw guar gum is hydrolyzed to a less viscous or non-viscous marketed product known as PHGG. The chain length of hydrolyzed guar gum can vary greatly, affecting the viscosity of the fiber supplement. While the high viscosity gel of raw guar gum is effective for both cholesterol lowering and improved glycemic control, partial hydrolysis will attenuate both the viscosity and the health benefits of guar gum. The degree of hydrolysis, and the resulting loss of gel-forming capacity, influence whether the marketed product will provide measurable health benefits.

Inulin is a naturally occurring fructose polymer (fructan) found in plants such as chicory root, onions, and Jerusalem artichoke. Inulin is well tolerated at doses less than 10 g/day, but may cause flatulence and other gastrointestinal symptoms at higher doses. The number of fructose units found in a given product can vary from 3 to 60 (note that fructans with a degree of polymerization less than 10 are called oligofructose). Inulin readily dissolves in water, and is readily fermented by bacteria in the gut.

Maltodextrin is a polymer of D-glucose units connected in chains of variable length. Maltodextrin is normally easily digested and absorbed as glucose. It can be purposefully converted to a resistant starch by rearrangement of starch or hydrolyzed starch from the normal *alpha*-1,4-glucose linkages (easily digested) to random 1,2-, 1,3-, and 1,4-*alpha* or *beta* linkages. Since the human digestive system effectively digests only *alpha*-1,4-linkages, the other linkages render the molecules "resistant" to digestion, hence resistant starch. Maltodextrin is soluble, non-viscous and readily fermented.

Methylcellulose is chemically treated (methyl chloride) cellulose, harvested from wood pulp. Cellulose is normally an insoluble fiber, but by treating the wood pulp with methyl chloride, the cellulose becomes soluble. While marketed as a bulk-forming laxative, with a caution not to use the product for more than 1 week unless directed by a doctor, the product might be recommended as a fiber supplement, so it was mentioned here. Methylcellulose is both soluble and viscous, but does not form a gel, so it does not significantly lower cholesterol, improve glycemic control, or exhibit other health benefits associated with gel-forming fibers.

Oat bran is a mixture of insoluble fiber and soluble fiber. The insoluble portion of oat bran has the potential to exhibit a laxative effect if the particle size of the marketed product has remained sufficiently large/coarse, and the dose is sufficiently large. The soluble viscous, gel-forming portion (β-glucan) can exhibit both a cholesterol-lowering effect in hyperlipidemia and improved glycemic control in type 2 diabetes, but only if processing has not destroyed the gel-forming capacity of the β-glucan. Recall the study above that assessed the cholesterol-lowering efficacy of cereals exposed to three different levels of heat and pressure during the extrusion process, and showed that with increasing heat/pressure, viscosity/gel-forming capacity was lost. β-glucan (3 g/day, about 1 1/2 cups of oatmeal) has FDA approval to claim a reduced risk of cardiovascular disease by lowering elevated serum cholesterol, but there is no specification for minimal gel-forming capacity. While oatmeal is obviously high in viscosity/gel-forming capacity, extruded cereals (e.g., heat/pressure extruded into specific shapes) and baked products may not retain a significant gelling capacity, yet can still make a health claim based on β-glucan. It is important to consider the degree of processing for a marketed product when considering potential for health benefits.

Polydextrose is a synthetic, indigestible glucose polymer that is soluble, non-viscous and readily fermented by the bacteria in the gut. The highly branched structure of polydextrose gives rise to a low hydrodynamic volume, which yields little effect on viscosity. Polydextrose is part of an emerging area of science related to the microbiome of the gut.

Psyllium, the seed husk of the Plantago plant, is a naturally occurring soluble viscous, gel-forming fiber that is not fermented by bacteria in the gut, so it retains its gelled nature throughout the digestive tract. Numerous well-controlled, randomized clinical studies show psyllium significantly lowers serum cholesterol in patients with hyperlipidemia, and reduces both fasting blood glucose concentrations and HbA1c in patients with Type 2 Diabetes and pre-diabetes (e.g., Metabolic Syndrome). As psyllium is not fermented and retains its gel throughout the large bowel, it acts as a stool normalizer, softening hard stool in constipation, firming loose/liquid stool in diarrhea, and reducing associated symptoms in both constipation and diarrhea. Psyllium is the only fiber recommended by the American College of Gastroenterology for improving symptoms of chronic constipation, and also is recommended for treating symptoms in patients with IBS.

Wheat dextrin is a soluble, non-viscous fiber formed by heating wheat starch (normally readily digested/absorbed in the small bowel) at high temperature, followed by enzymatic (amylase) treatment to form a resistant starch. Wheat dextrin is readily fermented in the large bowel, and does not form a gel, so it does not significantly lower cholesterol, improve glycemic control, or exhibit other health benefits associated with gel-forming fibers.

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