Pathogenesis of Colonic Diverticulosis: Repainting the Picture

First described in 1700, diverticulosis is now one of the most common gastrointestinal disorders in the Western world. More than 60% of adults older than age 60 have diverticulosis,1 with 4% to 25% of such individuals developing symptoms or complications (so-called diverticular disease).2 A plausible pathogenic hypothesis originally was proposed by Painter and Burkitt3 in 1971 (referred to here as Painter’s hypothesis). Consumption of a low-fiber diet results in small-volume, desiccated colonic contents that require the generation of high colonic pressures to progress toward the anus. High luminal pressures are thought to encourage the mucosa and submucosa to herniate through the circular muscle of the bowel at the point of greatest weakness, namely the site at which the blood vessels perforate the muscle layer, forming diverticulae. This pathogenic framework provides a ready explanation for the unequivocal association of diverticulosis with increasing age and Western lifestyle,4 and increasing prevalence in those migrating from a low-prevalence (African or Asian) to a high-prevalence (Western) region. It offers a simple preventive and possibly therapeutic option—increase dietary fiber intake. This tidy story, however, is being challenged.

There are 4 key aspects that support Painter’s hypothesis. First, epidemiologic features of diverticular disease support a strong association with dietary fiber intake. Diverticular disease is common in Western societies where fiber intake is low (15 g in the typical American diet) but is very uncommon in Africa or Asia where fiber intake is generally higher (35 g in the typical African diet). Other ecologic evidence includes observations that vegetarians have half the risk of asymptomatic diverticular disease than nonvegetarians5 and are 31% less likely to be hospitalized with diverticular disease compared with meat eaters.6 There is a 41% lower risk in those eating more than 25 g fiber/d compared with those consuming less than 14 g/d.7 Second, colonic physiological studies have indicated that higher colonic pressures are found in patients with diverticulosis than in healthy individuals.8 Experimentially induced colonic pressure in Painter’s experiments “distended [existing] diverticula to an alarming degree.”86 Subsequent studies addressing this yielded both supporting9–11 and negative results,12,13 probably related to small sample size, heterogeneity of the conditions, and area of the bowel studied. However, in patients with diverticulosis, the addition of dietary fiber decreased colonic pressures,14 although whether this decreases diverticular formation is unknown. Third, studies in animal models have strongly supported the hypothesis. A low-fiber diet also is associated with decreased colonic transit and decreased stool weight.15 Colonic diverticula develop in response to low- but not high-fiber diet in rats16 and in rabbits, where high colonic pressures were induced.17 The characteristic histopathologic changes associated with human diverticulosis, increased collagen and elastosis,18,19 also are observed in animals consuming a low-fiber diet.16 Fourth, several interventional studies have provided evidence in symptomatic (but not asymptomatic) disease for fewer episodes of diverticulitis, decreased rates of surgery, and overall improvement in global symptoms with administration of fiber, as outlined in Table 1. Unfortunately, the studies generally involved small numbers looking only at the symptomatic benefit, predominantly focusing on constipation, even though its association with diverticular disease was not established. However, in combination, they resulted in the recommendation for the consumption of a high-fiber diet. Currently, the American Dietetic Association recommends the average adult consume 20 to 35 g/d of fiber.20

Three lines of argument have challenged the Painter hypothesis. First, a pathogenic role of constipation is not well supported.21 Constipation and diverticular disease are highly prevalent in our community and thus commonly co-exist. Diverticular disease is found in approximately 6% of constipated patients21 and 16% of patients with diverticuloid disease described constipation.22 This is not markedly different from the background population prevalence of constipation.23 Second, there has been a recent flurry of research studies into alternative pathogenic hypotheses, suggesting that a neurologic or myopathic process may in fact underlie the disorder.24 Third, and most importantly, the inverse association of dietary fiber intake with diverticulosis has been questioned in epidemiologic studies (see later).

It is thus timely that, in this issue of Clinical Gastroenterology and Hepatology, Peery et al25 present a cross-sectional analysis examining the association between diet and diverticular disease. The dietary history of subjects with a new diagnosis of diverticuloid disease (539 cases) and without diverticuloid disease (1569 controls) were recorded within 3 months of undergoing a colonoscopy. Cases were newly diagnosed; this was of importance because the authors had been criticized previously for introducing bias by including patients with known diverticular diagnosis26 and included both symptomatic and asymptomatic patients. Patients with diverticuloid were older, more likely to be male, more likely to use tobacco or alcohol, and had a higher body mass index. More controversially, they were less likely to be constipated, less likely to report hard stools, and defecated more frequently. There was no association found between dietary fiber intake and diverticulosis.

Although this finding challenges current understanding, it is not entirely in isolation (Table 1). There are earlier studies with similar findings that have, until now, received only modest press. These studies27–29 in small numbers of patients from Asian populations (which have a very different diverticulosis phenotype compared with Western patients in that generally the right colon rather than the left colon is affected, raising the possibility of different etiologies) were colonoscopy-based and examined symptomatic and asymptomatic cases. Similar to the current study, they found no association with fiber intake but did find a positive association with meat and fat intake.

The Peery et al25 study is an important adjunct to these Asian studies because it is the largest worthy challenger to the existing evidence in the Western literature. It must, however, be viewed with caution. Despite its impressive outcomes, the cross-sectional nature of the study does not enable a causal relationship to be established. Indeed, the temporal relationship between diet and diagnosis also is difficult to ascertain. Dietary
assessments were completed within 3 months of colonoscopy but presumably years after the initial onset of disease. Although patients were not aware of a formal diagnosis of diverticulosis, some patients may still be self-medicating with high-fiber foods to treat symptoms associated with yet undiagnosed diverticular disease. Symptoms such as abdominal pain or constipation are readily self-treated with fiber in the community in the absence of a formal diagnosis. To their credit, the authors reported rates of abdominal pain between groups (and there was no difference), and the absence of a difference in dietary fiber supplement use between groups also argues against this proposition; yet one cannot exclude that dietary changes were not implemented years earlier by the patient in response to symptoms temporally remote from those collected in this study.

Most importantly, how this study is interpreted is limited by the overall low-fiber intake within the study population. Although the authors performed analyses stratified by fiber intake and found no significant difference between those in the lowest (2.5–10.1 g) and highest quartiles (18.4–50.3 g) of fiber intake, few patients in the uppermost quartile had a true high-fiber intake. This study should be applauded for challenging the status quo and refocusing attention on a common disease in which many questions remain unanswered. Although this study provides significant food for thought about how we recommend fiber to our patients, it does not provide enough evidence for a significant management change. Overall, there are still considerable benefits to fiber (such as preventing constipation or improving cholesterol management) with minimal risk. Based on the available evidence to date, we should continue to recommend a high-fiber intake as part of a healthy diet. Although this study is not yet the nail in the coffin for the fiber–diverticulosis theory, it does paint a different picture. Such a challenge to conventional wisdom

### Table 1. Overview of Studies Examining Dietary Fiber in the Prevention or Management of Diverticular Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of subjects</th>
<th>Design</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peery et al, 2012</td>
<td>2104 (878) a</td>
<td>Cross-sectional</td>
<td>Dietary history taken</td>
<td>High-fiber diet and increased frequency of bowel movements are associated with diverticular disease</td>
</tr>
<tr>
<td>Song et al, 2010</td>
<td>848 (103) a</td>
<td>Cross-sectional</td>
<td>Dietary history</td>
<td>Diverticulosis not associated with fiber intake</td>
</tr>
<tr>
<td>Lin et al, 2000</td>
<td>191 (85) a</td>
<td>Case-control</td>
<td>Dietary history</td>
<td>Right-sided diverticulosis is associated strongly with meat intake but no effect of fiber</td>
</tr>
<tr>
<td>Gear et al, 1979</td>
<td>320 (95) a</td>
<td>Case-control</td>
<td>Vegetarians vs nonvegetarians</td>
<td>Vegetarians had lower rates of diverticulosis; among meat eaters, those with the lowest fiber intake had the highest rates of diverticulosis</td>
</tr>
<tr>
<td><strong>Symptomatic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lander, 1972</td>
<td>55</td>
<td>RCT</td>
<td>High-fiber diet vs high fiber plus probiotic</td>
<td>Abdominal pain symptoms decreased by two-thirds in both groups</td>
</tr>
<tr>
<td>Aldoori et al, 1998</td>
<td>43,881 (385) a</td>
<td>Prospective cohort</td>
<td>Dietary history recorded</td>
<td>Fibre intake was associated inversely with risk of symptomatic diverticulosis</td>
</tr>
<tr>
<td>Smit et al, 1990</td>
<td>43</td>
<td>RCT</td>
<td>Fiber vs lactulose</td>
<td>Pain and symptoms improved in both groups</td>
</tr>
<tr>
<td>Manrousos et al, 1985</td>
<td>210 (100) a</td>
<td>Case-control</td>
<td>Dietary history</td>
<td>Those who regularly consumed vegetables were 50 times less likely to have diverticular disease in comparison with those who regularly consumed meat</td>
</tr>
<tr>
<td>Ornstein et al, 1981</td>
<td>58</td>
<td>RCT</td>
<td>Fiber vs placebo</td>
<td>Improved constipation symptoms only, no change in pain</td>
</tr>
<tr>
<td>Eastwood et al, 1978</td>
<td>31</td>
<td>Prospective intervention</td>
<td>Bran vs ispaghula vs lactulose</td>
<td>All interventions improved symptoms</td>
</tr>
<tr>
<td>Hodgson, 1977</td>
<td>30</td>
<td>RCT</td>
<td>Fiber vs placebo</td>
<td>Improvement in symptom scores with fiber compared with placebo</td>
</tr>
<tr>
<td>Brodribb, 1977</td>
<td>18</td>
<td>RCT</td>
<td>Fiber vs placebo</td>
<td>Improvement in symptoms with fiber</td>
</tr>
<tr>
<td>Taylor and Duthie, 1976</td>
<td>20</td>
<td>RCT</td>
<td>High-fiber diet vs laxative and antispasmodic vs bran</td>
<td>Bran most effective in improving symptoms</td>
</tr>
<tr>
<td>Plumley and Francis, 1973</td>
<td>48</td>
<td>Prospective intervention</td>
<td>High-fiber crisp bread</td>
<td>70% of patients symptoms were controlled with high fiber</td>
</tr>
<tr>
<td>Painter et al, 1972</td>
<td>70</td>
<td>Prospective intervention</td>
<td>High residue, low sugar + bran diet</td>
<td>88% of symptoms relieved or resolved</td>
</tr>
<tr>
<td><strong>Complicated</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Crowe et al, 2011</td>
<td>47,033 (812) a</td>
<td>Prospective cohort</td>
<td>Recorded dietary fiber levels</td>
<td>Fiber intake is associated with a decreased risk of hospitalization for diverticular disease</td>
</tr>
<tr>
<td>Colecchia et al, 2007</td>
<td>307</td>
<td>RCT</td>
<td>High fiber + rifaximin + high fiber alone</td>
<td>Both groups showed improvement with an additional benefit from rifaximin</td>
</tr>
<tr>
<td>Leahy et al, 1985</td>
<td>56</td>
<td>Retrospective cohort</td>
<td>Dietary history recorded</td>
<td>Patients with diverticulosis on a high-fiber diet were less likely to develop diverticulitis</td>
</tr>
<tr>
<td>Hyland and Taylor, 1980</td>
<td>100</td>
<td>Retrospective cohort</td>
<td>High-fiber diet</td>
<td>91% of patients on a high-fiber diet were symptom-free at 5 years</td>
</tr>
</tbody>
</table>

RCT, randomized controlled trial.

*aNumber of subjects are represented as cases with controls in parentheses.*
should maintain an open mind to alternative pathogenic mechanisms.

**References**