Epidemiology and Pathophysiology of Diverticular Disease

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ABSTRACT

Diverticular disease is common and thought to result from structural abnormalities of the colonic wall, disordered intestinal motility, or deficiencies of dietary fiber. Signs and symptoms of inflammation include fever, abdominal pain, and leukocytosis.

KEYWORDS: Diverticular disease, etiology, pathophysiology

Objectives: On completion of this article, the reader should be able to describe the epidemiology and pathophysiology of diverticular disease.

Diverticular disease includes diverticulosis or the presence of diverticula protruding through the colonic wall and diverticulitis, an acute inflammation of diverticula associated with fever, leukocytosis, and pain. The conditions annually account for 312,000 admissions and 1.5 million days of inpatient care in the United States.[1] Annual treatment costs in the United States exceed 2.6 billion dollars.[2]

HISTORY

Although diverticular disease is principally a condition that has become widespread in the 20th and 21st centuries, Alexis Littre, a French surgeon, first described it in the late 1700s.[3] In 1815, Fleischman[4] coined the term, divertikel, and Jean Cruveilheir[5] described herniations through the muscular layer of the colon in 1849. In 1869,[6] Klebs was the first to link the development of diverticula to constipation. Graser[7] described the inflammation of diverticula, known as diverticulitis in 1899. Mayo and his colleagues first described the surgical management of diverticulosis, but noted that most cases did not require invasive procedures.[8] Beer[9] correlated the clinical and histologic findings of the disorder in 1904; in 1914, Case[10] presented radiographic findings. In 1971, Painter and Burkitt published a milestone article delineating the role of dietary fiber in the prevention of diverticulosis.[11]

EPIDEMIOLOGY

Diverticular disease of the colon is common in developed nations. Westernized nations have high prevalence rates of left-sided diverticulosis. Right-sided diverticulosis although rare in Western populations, is more common in Asia, where overall rates of diverticula are much lower. Nonetheless, left-side diverticulosis is still more common in Asia. The presence of right-sided diverticula is considered a distinct disease from left-sided diverticulosis, and is thought to be due largely to genetic predispositions.[12]

Industrialization and development has been shown to increase rates of diverticulosis. In Singapore[13] and in Africa[14] urbanization has led to a higher prevalence of the condition. Rates of diverticulitis are also rising. In Finland, the incidence of diverticulitis has risen

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50% in the last two decades, largely in part to reduced dietary fiber and an aging population.[15]

The prevalence of diverticula in colon increases substantially with age. Under the age of 30, only 1 to 2% of patients have diverticulosis.[16] In early autopsy studies from the 1920s to the 1940s, overall prevalence was reported as 2 to 10%.[17] Prevalence increases to 50 to 66% in patients older than age 80 years.[18] Approximately 10 to 25% of patients with diverticulosis will develop diverticulitis.[19,20]

The prevalence of the disease in men is approximately equal to that of women. McConnell et al reported that diverticular bleeding occurs more commonly in men and strictures and obstructions occur more often in women.[21]

PATHOPHYSIOLOGY

The development of diverticula in the colon typically occurs in parallel rows between the taenia coli. The pathogenesis of the disorder involves three major areas: (1) structural abnormalities of the colonic wall, (2) disordered intestinal motility, and (3) deficiencies of dietary fiber. Additional factors have also been linked to diverticular disease.

Structural Abnormalities

The colon, unlike the small intestine and rectum, contains only one complete muscular layer, the inner circular layer. The outer longitudinal layer is concentrated in the three taeniae coli. Together these two layers form the muscularis propria. One of the taeniae coli is on the mesenteric aspect (taenia mesentericus) and the other two are located on the medial and lateral aspects of the bowel wall (taeniae omentalis and libra). The vasa recta, blood vessels from the mesentery, supply the mucosa and submucosal tissues.[22]

The colonic wall is weakest at the points between the mesenteric and antimesenteric teniae where the vasa recta penetrate the muscle. Microscopic studies have revealed muscle atrophy at these sites, which are naturally susceptible to herniation.[18] Diverticula often form at these areas of weakness, bulging through the circular muscle, but rarely through the taeniae.

As compared with healthy controls, the gross and microscopic anatomy of the colonic wall in patients with diverticular disease shows striking differences. Marked thickening of the circular muscle, shortening of the tenia, and narrowing of the lumen is seen in patients with diverticular disease.[23]

Thickening of the circular muscle is not due to muscle hypertrophy or hyperplasia, but instead from abnormal elastin deposition. Whiteway and Morson demonstrated that elastin content of the taeniae coli increases by greater than 200% in patients with diverticular disease compared with controls.[24] This leads to characteristic shortening of the muscle layer and an accordion-like effect known as concertina; it is found in the two-thirds of the bowel between the mesenteric and antimesenteric taeniae where diverticula are prominently found.[25]

Abnormal collagen cross-linking has been observed in the colonic walls of patients with diverticular disease. Increased levels of collagen cross-linking are seen in normal aging, especially after age 40 when rates of diverticulosis increase. When compared with age-matched controls, studies have shown that the patients with diverticular disease have greater rates of collagen cross-linking.[26]

The association of increased collagen cross-linking and the development of colonic diverticula is supported by the observation that patients with connective tissue disease such as Ehlers–Danlos or Marfan syndrome who have similar abnormalities of collagen cross-linking also develop diverticulosis earlier in life. It is hypothesized that increased collagen cross-linking decreases compliance leading to stiffer tissue that is more susceptible to tears, especially under conditions of increased luminal pressures.

Despite structural abnormalities of the colonic wall, a recent study has shown no differences in ion transport in patients with diverticulosis.[27]

Disordered Intestinal Motility

In the 1960s, Arfwidsson et al performed manometry on subjects with and without sigmoid diverticula, and showed higher luminal pressures in those with diverticular disease.[28] Painter and colleagues confirmed these results and performed simultaneous cineradiography. They discovered that under normal circumstances, haustral contractions occur simultaneously creating isolated compartments or "small bladders" that can generate locally high pressures.[29,30] This process is called segmentation. The researchers suggested that physiologically, segmentation aids in water reabsorption and electrolyte balancing, but could also cause locally increased pressures that could lead to herniation and the formation of diverticula. This effect can be increased by a lack of dietary fiber.[31]

Painter showed that the basal pressure of the sigmoid is a few millimeters of mercury above atmospheric pressure in both patients with and without diverticular disease. However, high pressure waves that normally have an amplitude of 10 mm Hg can have amplitudes as high as 90 mm Hg in patients with symptomatic diverticular disease.[30] High right-sided pressures are also associated with right-sided diverticular disease.[32] Although the associations are clear, it has been difficult for researchers to directly link high intraluminal

pressures to the development of diverticula due to inherent methodologic difficulties.[33]

Studies have shown that myoelectrical patterns differ in patients with diverticular disease compared with healthy subjects. Specifically, patients with diverticulosis exhibit slow wave motility patterns of 12 to 18 cycles per minute, distinctly different from the 3 cycles per minute pattern observed in irritable bowel syndrome.[33,34] Intake of bran normalizes motility patterns in patients with diverticular disease, but abnormal patterns persist after bran administration in patients with irritable bowel syndrome.[35]

In addition to myoelectrical aberrations, studies show hypermotility in the descending and sigmoid colon of patients with diverticular disease.[36] In 2001, Bassotti and colleagues performed 24-hour manometry on patients with diverticular disease and normal controls. They found that patients with diverticular disease displayed significantly increased amounts of motility in the affected segments compared with control subjects; in the diverticular disease group, response to a physiologic stimulus (meal) was also abnormal. They also observed increased amounts of disorganization and retrograde propagation of propulsions in the diverticular disease group.[37]

The complex role of chemical mediators on colonic motility in diverticular disease has been investigated. Tomita et al noted that the diverticular colon is more strongly innervated by cholinergic nerves than the normal colon; nonadrenergic, noncholinergic inhibitory nerves act to a lesser extent in the diverticular colon; and that nitric oxide mediates the relaxation reaction of nonadrenergic, noncholinergic inhibitory nerves to a lesser extent in the diverticular colon.[38] A study by Milner and colleagues revealed that vasoactive intestinal polypeptide (VIP) content of the mucosa and whole wall was increased in diverticular disease. They noted that VIP was unaltered in the circular muscle and taenia coli, and that substance P and neuropeptide Y levels in all layers of colonic wall were unaltered in diverticular disease.[39] A study by Costedio and colleagues evaluated the role serotonin (5-HT) plays in diverticular disease. Serotonin is known to be a primary trigger of gut motility. They found that serotonin levels were comparable in patients with and without diverticular disease, but that patients with a recent history of acute diverticulitis have significant attenuation of the 5-HT transporter, possibly accounting for delayed return of normal gastric motility after the resolution of inflammation in diverticulitis.[40] Although a large number of chemical mediators have been linked to colonic motility, their role in diverticular disease has not been well elucidated.

Dietary Fiber Deficiencies

In 1969, Painter and Burkitt popularized the theory that diverticular disease is due to a dietary deficiency in fiber, and that risks and rates of diverticulosis could be decreased by dietary changes. They studied over 1,200 individuals in the United Kingdom and in Uganda, and noted vast differences in diet, most strikingly in fiber intake. Longer stool transit times and lower stool weights were seen in the UK population, correlating with increased rates of diverticular disease.[11]

A wide body of evidence has emerged that supports this theory. Fiber is thought to lower intracolonic pressures, speed transit times, increase stool weight and volume, and contribute to more frequent bowel movements. The increased consumption of refined sugar and white flour, beginning in the Industrial Revolution coincided with decreases in dietary fiber intake. A sharp increase in diverticular disease in Western populations occurred ~40 years later, when the children first raised on the new "industrialized" diet became middle-aged.[41] Mendeloff criticized this theory as oversimplified,[42] and subsequent research has failed to show differences in stool transit time and volume between Westerners who have diverticular disease and those who do not. Researchers have found, however, a negative association between consumption of fiber and the development of diverticular disease.[43,44]

Animal studies done by Fisher and colleagues showed that only 9% of rats fed diets rich in fiber developed diverticulosis as compared with 45% of those fed a low-fiber diet.[45,46] Another animal model noted that rats fed high-fiber diets not only exhibited lower rates of diverticulosis, but were protected against collagen crosslinking in the colonic wall.[47] The same group noted that maternal diets rich in fiber were also associated in lower rates of diverticulosis in rat offspring.[47]

Studies have shown that in patients with diverticular disease implementing a diet high in fiber improves transit time in as little as 1 month.[48] Taylor and Duthie reported that after supplementing diverticular disease patients with bran tablets, stool weight increased, electrical rhythms improved, hypermotility decreased, and symptoms improved.[38]

Additional Factors

Several other factors have been suggested to play a role in the pathogenesis of diverticula.

INFLAMMATION

Although inflammation is certainly the major component of complicated diverticular disease, including diverticulitis, new evidence suggests that inflammation may also play a role in the early pathogenesis of the disease. Close examination of asymptomatic diverticula has revealed inflammation, without clinical evidence of diverticulitis,[49] and positive response rates to treatments with antiinflammatory medications such as mesalazine

and 5-ASA suggest that inflammation may play a larger role in pathogenesis than previously thought.[50]

NONSTEROIDAL ANTIINFLAMMATORY DRUGS

Nonsteroidal antiinflammatory drugs (NSAIDs) are associated with gastrointestinal complications, especially bleeding in the upper gastrointestinal tract. Studies suggest that NSAIDs are also linked with the development of diverticular disease and with complications of diverticular disease. Studies have shown that NSAID use in patients with complicated diverticular disease is nearly double the rate of NSAID use in patients with normal, healthy colons.[51] In addition, multiple studies have showed a clear link between NSAID use and an increased risk of diverticular hemorrhage.

SMOKING

The Health Professionals' Consortium Study did not find a relationship between smoking and the development of diverticular disease.[52] However, it has been suggested that smoking may increase the risk of complications of diverticular disease. Papagrigoriadis published data in which 53% of all patients with complicated diverticular disease smoked, whereas only 29% of patients with uncomplicated disease smoked.[53] However, two recent studies have failed to show a link between smoking and diverticular bleeding.[54,55]

PHYSICAL ACTIVITY/OBESITY

A lack of physical activity and the presence of obesity have been shown to increase the risk of diverticular disease. Aldoori and colleagues examined a prospective cohort of 47,678 American men, 40 to 75 years of age for a 4-year period and concluded that physical activity is inversely related to the development of diverticular disease, even when other factors such as fiber intake are controlled.[56] Strate et al followed 47,228 male health professionals between the ages of 40 to 75 years old and found that obesity increases the risks of diverticulitis and diverticular bleeding significantly.[57]

CAFFEINE AND ALCOHOL INGESTION

Because caffeine stimulates small bowel secretions and may affect colonic transit time, it has been suggested to play a role in the development of diverticular disease. A link between alcohol and diverticula has also been proposed. In a prospective cohort study of 47,678 American men, Aldoori and colleagues failed to show a link between either caffeine use or alcohol ingestion and diverticular disease.[58]

ROLE OF COLONIC FLORA

It has been postulated that fiber influences colonic microflora. Recently, the role microflora plays in the development and progression of diverticular disease has been the topic of debate. It has been suggested that altered microflora may predispose patients to microperforation and low-level inflammation by impairing mucosal barrier function and upregulating inflammatory cytokine release.[59] A study by Tursei et al randomized 90 patients with symptomatic diverticular disease into three arms: mesalazine, *Lactobacillus casei*, or both. The study found the combination treatment to be superior in preventing symptom recurrence.[60] A similar study comparing balsalazide, another aminosalicylate compound, and a complex of probiotics, found that the combination of balsalazide and probiotics was associated with increased remission rates at 12 months.[61]

DEVELOPMENT OF SYMPTOMS

Approximately 10 to 25% of patients with diverticular disease develop symptoms, ranging from acute diverticulitis to episodes of brief abdominal pain or alterations in bowel movements. Although the pathophysiology of symptomatic diverticular disease is unclear, research and theories have focused on interrelated processes including inflammation and visceral hypersensitivity.

Inflammation

The role of inflammation in the development of diverticular disease and progression of symptoms has been an increasing topic of discussion. It is clear that overt peritoneal inflammation associated with pain, leukocytosis, and fever is the hallmark of acute diverticulitis, but lower levels of chronic inflammation may also play a role in the pathogenesis of the disorder.

Horgan and colleagues reviewed 47 cases of sigmoid colectomy with primary anastomosis for chronic symptomatic diverticular disease or "smoldering diverticulitis."[62] Evidence of acute or chronic inflammatory changes was present in 76% of resected specimens. Complete resolution of symptoms occurred in 76.5%, with 88% being pain free.

Rarely, luminal mucosal inflammatory changes can be associated with diverticulosis, sharing features of inflammatory bowel disease. This disorder has been termed sigmoiditis, segmental colitis, and diverticular colitis.[63,64] Imperiali and colleagues recorded 5,457 consecutive colonoscopies at five participating institutions and found 20 patients (0.36%) met the endoscopic criteria for segmental colitis associated with diverticula. They noted that hematochezia was the main clinical feature, blood chemistries were generally normal, and the rectum was spared.[65]

Visceral Hypersensitivity

Visceral hypersensitivity refers to an excessive perception or response to stimuli. It has been suggested that such hypersensitivity may be responsible for symptoms in

diverticular disease, particularly the sharp episodic pain that patients often describe.[66]

Studies have shown that patients with acute diverticulitis have increase nerve staining in the muscularis propria, mucosa, and submucosa as compared with controls.[67] Nerve damage during inflammation with subsequent regeneration, proliferation, and hyperinnervation has been proposed as a mechanism for hypersensitivity.[68]

The exact mechanism between inflammation, hypersensitivity, and chemical mediators in the development of symptoms in diverticular disease is quite complex and is currently poorly understood. Future research should aim to elucidate this multifaceted biologic process to facilitate better prevention and treatment alternatives.

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