Epidemiology and Pathophysiology of Diverticular Disease

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Abstract

Keywords

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Colonic diverticular disease is a common health care issue which has historically been attributed to western countries and older age population. Recent studies have shown a rise in incidence among developing countries that have adopted western diets as well as rise in prevalence among younger patients. In this article, the authors discuss the incidence, epidemiology, and pathophysiology of colonic diverticular disease.

Diverticular disease of the colon is common in industrial countries and has significant impact on patient health as well as health care cost. Diverticular disease–associated hospital admissions have risen steeply in the recent past, which are not completely accounted for by the increasingly aging population of western countries. Approximately 130,000 hospitalizations occurring every year in the United States are attributable to diverticular disease.^{1–3} An analysis of the age-adjusted hospitalization rate of diverticulitis in the United States showed an increase from 62 per 100,000 in 1998 to 76 per 100,000 in 2005.⁴ These admission rates increased most in younger patients (< 45 years old) and have remained unchanged in patients older than 65 years.

Incidence and Epidemiology

The prevalence of diverticular disease is similar between men and women. However, it increases significantly with age, ranging from 10% in those younger than 40 years up to 50 to 70% in those older than 80 years.^{2,5,6} The anatomic distribution of diverticulosis in the colon also varies by geographic locations. In individuals that reside in western industrialized nations, the diverticula are limited to just the sigmoid colon in 65%, sigmoid plus other colonic diverticula in 25%, pan colonic diverticula in 7%, and diverticula isolated to a segment proximal to the sigmoid colon in 4% of patients.⁷ In Asian population, the anatomic distribution is different and primarily involves the right colon with a prevalence rate of approximately 13 to 25%.^{8–11}

There is also evidence to suggest that distribution of diverticulosis varies by race. A recent study that performed a prospective analysis of 624 patients undergoing screening colonoscopy at a single institution between the years 2013 and 2015 found that while sigmoid colon still remained the most common location for formation of diverticula for both Caucasian and African American races, the latter had a higher rate of diverticula in ascending colon and hepatic flexure compared with Caucasians, where descending colon was most often involved.¹²

Although it is well documented that prevalence of diverticulosis increases with age, multiple studies in the past decade have been looking at incidence and disease progression in younger patients who present with diverticulitis. A population study that looked at a nationwide inpatient sample between the years 1998 and 2005 and analyzed 267,000 patients admitted with acute diverticulitis.¹³ The results of the study showed an overall 26% increase in admission for diverticulitis from the year 1998 to 2005. The rates of admission increased more rapidly in patients aged 18 to 44 years compared with older patients (82 vs. 36%, respectively). A similar observation was made in prospective analysis of 207 patients hospitalized at a single institution with diverticulitis between the ages of 27 and 92 years with mean age of patients being 61 years and found that 25 of the patients were younger than 45 years. The study found that diverticulitis in young patients has a male predominance and a more aggressive course with higher rate of complications and higher recurrence rate.¹⁴

Potential Contributing Factors to Diverticular Disease

Lack of Fiber

Epidemiologic studies show that there are certain factors that are associated with an increased risk of developing diverticulosis or diverticular disease. Multiple studies have looked at dietary influences in development of diverticulosis as well as risk of diverticulitis.^{15–18} There is a long-held theory that a diet rich in fiber protects against the development of diverticular disease after Painter and Burkitt hypothesized it in their article in 1960s and 1970s.¹⁹ They based their hypothesis on the observation that individuals in different geographic locations such as western industrialized countries versus those in developing countries were noted to have different rates of prevalence. They postulated that those in industrialized nations tended to eat processed food that was low in fiber compared with individuals in Africa and Asia, where the disease was previously unknown.

Other studies have also observed that African Americans and Japanese immigrants in western countries developed diverticular disease at similar rates as native westerners.^{17,20} In a cohort study that looked at more than 47,000 men, total dietary fiber intake was noted to be inversely associated with risk of symptomatic diverticular disease (relative risk [RR] = 0.58).²¹

On the contrary, other studies have shown either no effect of dietary fiber intake or an even positive correlation between fiber intake and diverticulosis.^{22–25} This contradicting information in the literature is a testament to the difficulty in proving correlation due to the complex methodology for monitoring dietary habits in combination with long latency of diverticula formation. For the time being, there is a consensus in the presence of significant benefit that is obtained from fiber for overall health of patients and should continue to be recommended as part of daily diet.²⁰ The Dietary Reference Intakes recommends consumption of 14 g of dietary fiber per 1,000 kcal of diet, or 25 g for adult women and 38 g for adult men.

Nuts, Corn, Grains, and Popcorn

Patients with diverticulosis historically used to be advised to avoid eating nuts, corn, popcorn, and seeds in an attempt to reduce the risk of diverticular disease. However, there is little evidence to support this theory. Strate et al performed the Health Professionals Follow-up Study which consisted of a cohort of men followed up prospectively from 1986 to 2004 via self-administered questionnaires. This study, which had an 18 years follow-up and included 47,228 men between the ages of 40 and 75 years, found an inverse relationship between nut/popcorn consumption and the risk of diverticulosis or development of diverticular disease.¹⁶ Hence, nuts, corn, grains, and popcorn are safe to consume in patients with known diverticula without the risk of increasing risk of diverticulitis.

Red Meat and Fat Consumption

A diet rich in red meat consumption has been shown to have a correlation with increase in incidence of symptomatic

diverticular disease. The mechanism by which red meat can lead to symptomatic disease is not well understood, yet observational studies have shown a 1.5 to 2 times increase in risk.^{18,25} A cross-sectional colonoscopy supported study of 2,104 patients found the risk of diverticular disease to be significantly increased in diets that were high in total fat or red meat and low in fiber (RR: 2.35 vs. 3.32).²⁵

Physical Activity and Obesity

After adjustment for age, dietary fat, and fiber intake, studies that have looked at effect of exercise on the development of diverticular disease show that physical activity has a protective effect in the risk of developing symptomatic diverticular disease.^{25–27}

Similarly, obesity has been associated with an increased risk in development of both diverticular bleeding and diverticulitis.^{27,28}

Alcohol and Caffeine

Although there are some literatures, mostly observational studies, that raise the possible relation of alcohol to diverticular disease, there is currently no conclusive and convincing evidence that there is a direct relationship between alcohol or caffeine consumption and symptomatic diverticular disease.^{16,29–32}

Medications

Multiple medications have been reported to be associated with diverticular disease. Regular use of nonsteroidal anti-inflammatory drugs has been associated with increased risk of diverticular bleeding as well as complicated diverticulitis, especially perforation.^{33,34} The same literature also suggest an increased risk of diverticular disease in patients taking steroids and opiates.

Among patients with diverticulosis, higher levels of serum vitamin D have been associated with significantly lower risk of diverticulitis.¹⁸ There is evidence to suggest that statins may have a protective effect against diverticular perforation in patients with diverticulosis.

Pathophysiology of Formation of Diverticula

Colonic diverticula are false or pulsion diverticulum that contain outpouching of only the mucosal and muscularis mucosal layers. Most patients with diverticulosis are asymptomatic and are frequently found on routine screening colonoscopies with approximately 25% of them progressing to a symptomatic disease during their lifetime.¹

Diverticula develop at points of weakness in a colonic wall where vasa recta penetrate the circular muscle layer to deliver blood to the colonic mucosa. As previously mentioned, low-fiber diet, structural abnormalities, and aging are traditionally implicated in the development of diverticular disease. The pathogenesis of symptomatic diverticular disease is complex with factors such as chronic low grade inflammation, alteration of intestinal microflora, as well as alteration in motility playing a role in the development of the disease.

Chronic Low-Grade Inflammation

Symptomatic diverticular disease has been shown to manifest significant microscopic inflammatory cells, predominantly lymphocytes and neutrophils, which seem to be associated with the severity of the disease.^{35–37} Horgan et al have reported in their study that looked at resected colonic specimens that 75% contained chronic inflammation around the diverticula.³⁸

Abnormal Colonic Motility

In recent years, multiple studies have hypothesized the role of abnormal colonic motility as a key factor in the pathophysiology of formation of diverticula.^{39–43} These studies postulate that derangement of enteric innervation (especially related to interstitial cells of Cajal and enteric glial cells), mucosal neuropeptides such as serotonin, and acetylcholine in combination with mucosal inflammation plays a significant role in the formation of diverticula.

Serotonin is an important neuroendocrine transmitter participating in the control of motor activity through neural and biochemical mechanisms in the enteric nervous system. Banerjee et al examined 16 colonic specimens with sigmoid diverticular disease that were compared with sections of bowel without diverticula from the same specimens. Their result showed the increased presence of serotonin cells in the diseased segment of colon, which supported the hypothesis that this may be contributing to the pathogenesis of the condition by altered colonic motility.^{39,43} Other studies have implicated upregulation of acetylcholine and nitrergic neuromuscular transmission in playing a role in colonic motor disorders associated with diverticular disease.⁴¹

High Colonic Intraluminal Pressure

According to the law of Laplace, pressure is directly proportional to wall tension and inversely proportional to bowel radius. Sigmoid colon has the smallest bowel diameter, which means it has the tendency to create the highest luminal pressure. Such increase in pressure in combination with altered colonic motility is hypothesized to play a role in the formation of diverticula.

Genetic Predisposition

Some genetic disorders that are related to connective tissue disorders such as Ehlers–Danlos's disease and polycystic kidney disease and Saint's triad (triad of gallstones, colonic diverticula, and hiatal hernia in elderly) have been postulated to be associated with predilection to formation of diverticula.³⁸ However, the body of evidence is not conclusive because there is inadequate data to show convincing direct correlation. Further basic science research is needed to explore this hypothesis.

Other Gastrointestinal Diseases

There is a body of evidence that has postulated a relation between irritable bowel disease and development of diver-

ticulosis. Jung et al performed a population-based cross-sectional survey through a validated symptom questionnaire of 1,712 patients who had undergone at least one relevant study, such as colonoscopy, computed tomography scan, or barium enema. After adjusting for age and gender, the presence of irritable bowel syndrome (IBS) was associated with an increased odd for diverticulosis (odds ratio [OR] = 1.8, 95% confidence interval [CI]: 1.3–2.4). In patients older than 65 years, the presence of IBS was associated with a ninefold increase in the presence of diverticulosis (OR = 9.4, 95% CI: 5.8–15.1).⁴⁴

Pathogenesis of Diverticulitis

The direct pathogenesis and progression of diverticulosis to diverticulitis are also not clear. Diverticulitis is the inflammation of a diverticulum or diverticula accompanied by gross or microscopic perforation.

One possible hypothesis is similar to pathogenesis of appendicitis where stasis or obstruction in the narrow necked pseudodiverticulum leads to bacterial overgrowth and local tissue ischemia leading to microperforation.² Approximately 4 to 15% of patients with diverticulosis will develop diverticulitis, which has traditionally been believed to increase with age.^{13,45–47}

The proper classification of the severity of the diverticulitis is critical since it will determine the treatment modalities. One most commonly used method is a Hinchey's classification, which was first published by Hinchey et al in 1978.⁴⁸ Hinchey's system categorizes severity of diverticulitis into four stages (► **Table 1**).

The Hinchey Stage I disease can be treated with bowel rest and antibiotics. Stage II might or might not require drain placement depending on size of abscess. Stages III and IV generally require operative intervention. Besides guiding treatment options, this system allows easy and clear communication among health care professionals regarding disease severity.

Despite having such classification system, there are still segments of patients where diagnosis and management of diverticulitis can be challenging. One such subgroup is patients receiving immunosuppression therapy since they are at a double disadvantage where their symptoms are masked by the same medications that impair their ability to fight the infection. Several studies have shown increased mortality associated with diverticulitis in immunocompromised patients. A recent study published by Brandl et al which was a retrospective study of 227 patients who received treatment for diverticulitis at a single institution showed the

Table 1 Hinchey classification of severity of diverticulitis

Hinchey stages	Clinical or radiographic finding
Stage I	Pericolic abscess
Stage II	Pelvic or retroperitoneal abscess
Stage III	Generalized purulent peritonitis
Stage IV	Generalized fecal peritonitis

morbidity and mortality due to sigmoid diverticulitis to be significantly higher in immunosuppressed patients. Immunosuppressed patients had longer hospital stay (27 vs. 14.5 days, $p = 0.016$), higher rate of emergency operation (66 vs. 29%, $p = 0.004$), and higher in-hospital mortality (20 vs. 4.7%, $p = 0.045$).⁴⁹

Conclusion

Diverticular disease remains one of the most common diseases of the gastrointestinal tract in western countries and is showing an increasing incidence in younger patients as well as developing countries that have started adopting western diets. Despite its prevalence, its pathophysiology still remains poorly understood. Most of our understanding of the disease results from theories and hypothesis, which often have contradicting conclusions. Complex interaction among diet, colonic motility abnormalities, genetic influences, and other bowel diseases are believed to play a role. There is significant need for more basic science research on this topic to help improve our understanding of risk factors and disease progression.

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