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Modifiable risk factors for the development and severe course of diverticular disease: a review

Authors:
Natalia Niderla
Uniwersytet Medyczny w Lublinie
natalia.niderla@yahoo.pl
https://orcid.org/0009-0001-5041-7846

Jakub Klohsek
Uniwersytet Medyczny w Lublinie
jakub.klohsek@gmail.com
https://orcid.org/0009-0009-9644-3538

Introduction and purpose:
Diverticulosis is a common condition of the bowel, particularly affecting the sigmoid colon with age-dependent increase in prevalence. While often asymptomatic and discovered incidentally during colonoscopies or imaging, some patients experience symptoms like left lower abdominal pain, bloating, and irregular bowel habits. When symptoms arise, it is termed diverticular disease (DD). Approximately 10% of diverticulosis cases progress to diverticulitis, which involves inflammation and can lead to complications like abscesses, perforation, or obstruction. In the U.S., acute diverticulitis accounts for 200,000 hospitalizations annually, costing about $2.2 billion in healthcare. The purpose of this paper is to review the current understanding of modifiable risk factors associated with the development and progression of diverticular disease
Materials and methods: Our research was based on analysis of PubMed and Google Scholar databases, using key search terms "diverticulosis," "diverticular disease," "diverticulitis," "diverticular hemorrhage," and "risk factors."

Conclusions:
Several lifestyle and dietary factors contribute to the onset and progression of diverticular disease and diverticulitis. A low-fiber diet increases the risk by slowing gut motility and raising pressure in the colon, while a high-fiber diet helps protect against the disease. Obesity, physical inactivity, and smoking also increase the risk, with regular exercise offering protective benefits. High red meat consumption and excessive alcohol intake are linked to higher incidences of diverticulitis, while NSAID use raises the likelihood of complications. Additionally, low vitamin D levels are observed in patients with severe diverticulitis, though the role of supplementation remains unclear.

Keywords: diverticulosis, diverticular disease, diverticulitis, diverticular hemorrhage, risk factors

Introduction

Diverticulosis is a common condition, which prevalence increases with age. In Western countries it affects approximately 5% of individuals in their 40s, 50% of those in their 60s, and up to 70% of those in their 80s.[1] It is defined as a structural abnormality of the bowel with submucosal herniations through weak areas of the smooth muscle, most common in the sigmoid colon.[2,3] The disease is often asymptomatic and is usually detected incidentally during preventive colonoscopies or imaging of the abdominal cavity for other reasons. Some of the patients can develop clinical symptoms including: chronic abdominal pain located in the left lower quadrant, diarrhea, constipation, bloating.[4] When symptoms of diverticulosis appear, we can refer to it as diverticular disease (DD). In symptomatic uncomplicated diverticular disease there are no signs of systemic inflammation (normal WBC and CRP levels), but high fecal calprotectin levels may indicate local inflammation.[5] About one in 10 patients with diverticulosis will develop diverticulitis - inflammation of a diverticulum, which manifests as severe episode of abdominal pain, low grade fever, leukocytosis, tachycardia, hypotension.[4,6,7] Among the possible complications of diverticulitis are abscess, perforation, stricture, obstruction, fistula, segmental colitis.[8] In the United States, acute diverticulitis leads to approximately 200,000 hospital admissions each year, with annual healthcare costs reaching around 2.2 billion dollars.[9]

Pathophysiology

The pathophysiology of diverticular disease remains incompletely understood, though genetic predisposition is thought to play a significant role. Research has identified associations between DD and specific single nucleotide polymorphisms (SNPs) in genes such as *COL3A1* (encoding type III collagen), *TNFSF15* (a TNF family cytokine), *RPRM* (Reprimo, a protein involved in DNA repair and cell cycle regulation), and *LAMB4* (a laminin subunit β4, a constituent of the extracellular matrix).[1] Genetic susceptibility appears to significantly influence DD development, as supported by migration studies showing stable incidence rates among populations, even when lifestyles and dietary habits shift.[2] This aligns with anatomical patterns observed worldwide: in Western countries, diverticulosis predominantly affects the left colon, whereas in Asian populations, it is more common in the right colon.

Interestingly, among Japanese individuals residing in Hawaii, the prevalence of right-sided diverticula persists despite the adoption of a Westernized diet.[10] Further evidence of genetic influence is seen in twin studies, where the odds of developing diverticular disease are 7.15 times higher in monozygotic twins if their sibling is affected, compared to 3.20 times higher in dizygotic twins.[11] The enteric nervous system (ENS), a component of the autonomic nervous system, plays a crucial role in regulating gastrointestinal functions independently of the brain and spinal cord.[12] In patients with diverticular disease research has demonstrated a marked reduction in the density of enteric neurons, glial cells, and intramuscular nerve fibers.[13] This decrease in ENS structures suggests a neuropathic component to DD that impacts both intestinal structure and function. The implications of this ENS dysfunction in DD are likely twofold. First, the reduced and abnormal innervation within the intestine may lead to impaired motor function. Studies analyzing intestinal tissue from DD patients have identified atypical responses in intestinal muscle contractility to neurotransmitters like nitric oxide, tachykinins, substance P, endocannabinoids, and acetylcholine. These findings indicate that structural changes in the ENS contribute directly to functional impairments, leading to abnormal intestinal motility and contractile behavior. Secondly, the dysfunction of the ENS may underlie some of the symptoms associated with DD, as a compromised ENS would struggle to regulate the coordinated movements and signaling required for normal digestive function.[14] Multiple environmental risk factors have been proposed in the development of diverticular disease, and the findings on their impact will be discussed in this review.

Non-Fiber diet

Research indicates that dietary habits are a crucial factor in determining the diversity of gut microbiota and fiber intake is a big part of that.[15] Additionally, a high-fiber diet accelerates intestinal motility while reducing pressure in the intestinal lumen. There is a negative correlation between the diversity of gut microbiota and the incidence of chronic diseases such as inflammatory bowel disease (IBD), colorectal cancer (CRC) and obesity.[16] High intake of dietary fiber has been linked to a reduced risk of diverticular disease, with diets rich in fruit and cereals offering the most protection.[17] In multicenter study involving patients with uncomplicated symptomatic diverticular disease, participants were divided into two groups. Group A received one daily sachet of Flortec© (Lactobacillus paracasei B21060) alongside a high-fiber diet for six months, while group B followed only a high-fiber diet. In group A, the proportion of patients experiencing abdominal pain decreased from 100% at baseline to 25% after six months. In group B, this proportion decreased from 90.5% to 38.1%. However, no reduction in bloating was observed in group B.[18] In another study participants in the highest quintile of fiber intake exhibited a significantly lower relative risk of both complicated and uncomplicated diverticular disease compared to those in the lowest quintile.[4] The EPIC-Oxford study, which followed over 47,000 individuals for an average of 11.6 years, confirmed these findings. Participants in the highest fiber intake group had a similarly lower risk of hospitalization or death from diverticular disease compared to those with the lowest fiber intake (<14 g/day).[19] However, there are also studies that link high fiber intake with an increased incidence of diverticular disease.[20,21]

Obesity

Obesity has been recognized as a 21st-century epidemic, with its global prevalence continuing to rise at an alarming rate. This condition significantly contributes to the development of various diseases encompassed within the metabolic syndrome, including type 2 diabetes, dyslipidemia, hypertension, and cardiovascular disorders.[22] Research also indicates a significant correlation between obesity and diverticular disease. In a large-scale cohort study spanning 248,001 person-years of follow-up, 1,084 cases of diverticulitis were documented, demonstrating a linear relationship between body mass index (BMI) and the risk of developing diverticulitis. Additionally, an elevated BMI was identified as a risk factor for diverticular bleeding.[23] Further evidence from a meta-analysis revealed that for every 5-unit increase in BMI, there was a 28% rise in the relative risk of diverticular disease, a 31% increase in the risk of diverticulitis, and a 20% increase in the risk of complications associated with diverticular disease.[24]

Low level of physical activity

Recent research has shed light on the protective effects of physical activity against diverticular disease. A large-scale, prospective study explored this association over an 18-year follow-up period. Throughout the study, 800 cases of diverticulitis and 383 cases of diverticular bleeding were documented. The findings highlighted a clear link between higher levels of physical activity and a lower risk of both conditions. Specifically, men who ranked in the highest quintile of total physical activity had a 25% lower risk of developing diverticulitis and a 46% lower risk of experiencing diverticular bleeding compared to men in the lowest quintile.[25] Another study conducted survival analyses over a 7.7-year follow-up, involving 9072 men and 1664 women from an older adult cohort (aged 50 and above). This study captured 84% of the original population and assessed the impact of both regular running distances and 10-kilometer footrace performance, the latter serving as an indicator of cardiorespiratory fitness. Adjustments were made for age, sex, and dietary factors, including the consumption of meat, fish, fruit, and alcohol. The data revealed that for each additional kilometer run per day, the risk of developing diverticular disease dropped by 6.2%. Furthermore, individuals who ran more than 8 kilometers per day had a 48% reduced risk compared to those who ran 2 kilometers or less. Performance in the 10-km race also played a significant role: each 1 m/s increase in running speed corresponded to a 36% decrease in disease risk. Remarkably, those who ran faster than 4 m/s exhibited a 70% lower risk of diverticular disease compared to individuals who ran at speeds of 2.8 m/s or slower. This reduction in risk persisted even when researchers adjusted for baseline body mass index and usual running distance. These findings underscore the importance of regular and vigorous physical activity, not only for overall health but also for reducing the likelihood of diverticular complications.

Red meat

Numerous health organizations, including the World Health Organization, the U.S. Departments of Health and Human Services and Agriculture, the EAT-Lancet Commission,

advocate for reducing red meat consumption.[26] This guidance is supported by a growing body of scientific research suggesting that high intake of red meat, especially when processed, may be linked to an elevated risk of several chronic conditions, such as type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), and various forms of cancer.

Moreover, higher red meat consumption is associated with an increased risk of overall mortality.[27] Research also points to a potential connection between red meat consumption and the risk of developing diverticular disease. Supporting this, the Health Professionals Follow-up Study (HPFS), an extensive ongoing prospective cohort study, has followed 51,529 U.S. male health professionals aged 40 to 75 since their enrollment in 1986. Participants receive biannual questionnaires that gather information on demographics, lifestyle habits, medical history, and disease outcomes, while dietary intake is reassessed every four years. Impressively, the study maintains a follow-up rate exceeding 94%. Over the course of 651,970 person-years of monitoring, 764 new cases of diverticulitis were identified. Men in the highest quintile of red meat consumption had a multivariable relative risk (RR) of 1.58 compared to those in the lowest quintile. Notably, the increased risk showed a non-linear trend, leveling off after the consumption of six servings per week. The link was found to be stronger for unprocessed red meat than for processed varieties.[28]

Alcohol

Despite its well-documented harmful effects on virtually all systems in the body, alcohol is one of the most popular drugs in the world.[29] A potential mechanism linking excessive alcohol consumption with an increased risk of diverticular disease is a decrease in intestinal prostaglandin synthesis.[30] It was found in large prospective study of women that women in the highest alcohol consumption category (at least 2 drinks per day) had a significantly higher risk of diverticulitis.[31] In another cross-sectional study involving 6,180 individuals, the prevalence of diverticulosis was 7.3%. Analysis revealed that one distinguishing factor between individuals who developed diverticular disease and those who did not, was an increased alcohol intake.[32] In a separate cohort study conducted in Taiwan, utilizing the national health system database, a group of over 50,000 individuals recently diagnosed with alcohol intoxication was created, alongside a cohort of over 200,000 randomly selected individuals with no history of alcohol intoxication. Individuals with a prior diagnosis of diverticular disease were excluded from the study. The cohort was observed over an 11-years period. After this time, the data indicated that regardless of gender or other factors, the risk of diverticular disease was significantly higher in the alcohol cohort compared to the control group.[33] Similar results were obtained in another prospective study involving 848 patients in Korea.[34]

Smoking

Smoking tobacco is a significant risk factor for various gastrointestinal conditions, including Crohn's disease, peptic ulcers, and gastroesophageal reflux disease. Moreover, epidemiological studies have indicated a potential link between smoking and the development of colonic diverticulosis.[35] The growing body of evidence highlights how smoking may influence not only the onset but also the progression and severity of diverticular disease. A

population-based comparative cohort study focused on patients admitted to hospitals with diverticulitis. Using data from the Discharge Abstract Database, researchers analyzed 176 adults who were emergently hospitalized for diverticulitis in Calgary between 2009 and 2010. Among patients diagnosed with diverticulitis, smoking status significantly influenced the likelihood of requiring surgical intervention. Specifically, 26.8% of these patients were current smokers, 31.5% were former smokers, and 41.6% had never smoked.
Compared to non-smokers, current smokers had an adjusted odds ratio of 9.02 (95% CI: 2.47–32.97) for needing surgery, while former smokers had an adjusted OR of 5.41 (95% CI: 1.54–18.96).[36] Another retrospective study reviewed medical records of 261 patients who underwent elective surgery for diverticular disease at Helsinki University Central Hospital over five years. The findings were striking: smokers required sigmoidectomy at a significantly younger age than their non-smoking counterparts. Additionally, smoking was associated with a higher incidence of bowel perforations and a greater likelihood of postoperative recurrent diverticulitis episodes.[37] These results emphasize the significant impact of smoking on the severity and management of diverticulitis, highlighting smoking as a crucial factor in the diverticular disease's progression. Furthermore, a comprehensive meta-analysis synthesized data from observational studies examining the relationship between smoking and diverticular disease. The analysis revealed a 36% increase in the relative risk (RR) for current smokers, a 17% increase for former smokers, and a 29% increase for individuals who had ever smoked. The research also highlighted an elevated risk for diverticular disease complications among smokers. A linear dose-response assessment indicated an 11% (though statistically nonsignificant) rise in RR for every additional 10 cigarettes smoked per day.[38] Collectively, these studies underscore the detrimental impact of smoking on the development and clinical outcomes of diverticular disease. The evidence points to smoking as a modifiable risk factor, with clear implications for both prevention and management strategies aimed at reducing the burden of this gastrointestinal condition.

NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a class of medications commonly used to treat pain, fever, and other inflammatory processes. Their main mechanism of action is the inhibition of the enzyme cyclooxygenase. There are many known side effects of NSAIDs. In the digestive system, they reduce the synthesis of prostaglandins that protect the gastric mucosa, contributing to the development of peptic ulcer disease.[39] Regular use of NSAIDs is also associated with an increased risk for diverticulitis and diverticular bleeding.[40] In a large case-control study, investigators identified patients, who were admitted to hospitals in Norfolk, UK, between April 1995 and February 2000 with ICD-10 diagnosis: K57.2 (perforation, abscess or peritonitis of large intestinal diverticula), K57.4 (perforation, abscess, peritonitis of both small and large bowel diverticula) and K57.8 (perforation, abscess, peritonitis of either small or large bowel diverticula). Two control groups were also created and data on medications used by patients were collected. Use of NSAIDs showed a significant positive association with diverticular perforation, whereas no association was found with aspirin.[41] Another large prospective cohort study examined the effects of regular NSAID and aspirin use on the risk of diverticulitis and diverticular bleeding. Approximately 50,000 men

completed a comprehensive questionnaire detailing their medical history and dietary habits. Every four years, participants updated their health status through follow-up questionnaires. At baseline, 29% of participants reported regular use of aspirin, while 5% reported regular use of NSAIDs. During 859,164 person-years of follow-up, there were 939 documented cases of incident diverticulitis and 256 cases of diverticular bleeding. The study found a significantly higher risk of diverticulitis among regular NSAID users (HR = 1.72) and a moderately increased risk among regular aspirin users (HR = 1.25) compared to non-users of these drugs. Additionally, regular NSAID use was more strongly associated with the risk of complicated diverticulitis (HR = 2.55) than with uncomplicated diverticulitis (HR = 1.65) compared to those who did not use NSAIDs or aspirin. For diverticular bleeding, both NSAIDs and aspirin showed similar associations (HR = 1.74).[40] In a separate study, 51 patients who had been hospitalized for diverticular hemorrhage were identified and analyzed. By comparing various risk factors with a control group, the study demonstrated that the use of NSAIDs was associated with a substantially elevated risk of diverticular hemorrhage, increasing the likelihood by as much as tenfold.[42]

Vitamin D deficiency

Maguire et al. conducted a retrospective cohort study that compared pre-diagnostic serum 25(OH)D levels between patients with uncomplicated diverticulosis and those hospitalized with diverticulitis.[43] Patients with diverticulitis had significantly lower vitamin D levels (25.3 ng/mL) compared to those with uncomplicated diverticulosis (29.1 ng/mL). Among diverticulitis subtypes, vitamin D levels were consistently lower, particularly for patients requiring emergent laparotomy (22.7 ng/mL) and those with recurrent diverticulitis (23.5 ng/mL). These findings were further substantiated by a second large-scale study that established an association between reduced ultraviolet light exposure and the incidence of diverticulitis.[44] However, another large, randomized, double-blind trial involving over 5,000 participants demonstrated that the risk of hospitalization due to diverticular disease was very similar in the group receiving 100,000 IU/month vitamin D supplementation compared to the placebo group.[45]

Conclusions

In conclusion, several critical lifestyle and dietary factors have been identified as playing a role in the onset and progression of diverticular disease and diverticulitis. A low-fiber diet, which slows gut motility and raises intracolonic pressure, is associated with an increased risk of developing diverticular disease. A high-fiber diet seems to offer protection, likely by fostering a healthier gut microbiota and reducing inflammation. Obesity is also a major risk factor, with each 5-unit rise in BMI linked to a higher likelihood of complications in both diverticular disease and diverticulitis. Additionally, physical inactivity is associated with an elevated risk of diverticulitis and diverticular bleeding, while regular, vigorous physical activity has been shown to have protective benefits. High red meat intake, especially of unprocessed varieties, is correlated with a higher incidence of diverticulitis, with risk plateauing at around six servings per week. Similarly, excessive alcohol consumption is linked to a heightened risk, potentially through its effects on gut barrier integrity. Smoking is

another modifiable factor, as it is associated with more severe forms of diverticular disease and a greater likelihood of complications, such as perforations and the need for surgical intervention. The regular use of NSAIDs also increases the risk of complications like perforation and bleeding, likely due to their impact on protective gut prostaglandins. Finally, low vitamin D levels have been observed in patients with severe or recurrent diverticulitis, although large-scale studies provide mixed evidence on whether vitamin D supplementation significantly impacts diverticular disease outcomes. Overall, these findings emphasize the importance of a balanced diet, weight management, regular physical activity, and cautious use of medications like NSAIDs to reduce the risks of diverticular disease and its complications.

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Author'scontribution:

Conceptualization: Natalia Niderla
Formal analysis: Natalia Niderla, Jakub Klohsek
Investigation: Natalia Niderla, Jakub Klohsek
Resources: Natalia Niderla, Jakub Klohsek
Data Curation: Natalia Niderla, Jakub Klohsek
Writing -rough preparation: Natalia Niderla
Writing -review and editing: Natalia Niderla, Jakub Klohsek
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Supervision: Natalia Niderla, Jakub Klohsek

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