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# Does Subclinical Inflammation Play a Role in the Pathogenesis of Diverticulosis?

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Colonic diverticulosis, the presence of outpouchings from the colonic lumen, affects more than 50% of individuals by age 60 in the United States.[1] Although generally asymptomatic, patients with diverticulosis may experience complications, including diverticulitis (sometimes leading to perforation, abscess, or peritonitis), fistula, stricture, obstruction, or bleeding.[2] Complications associated with diverticular disease were among the leading gastrointestinal indications for hospitalizations and outpatient clinical visits, imposing a significant burden on patients and the US health care system.[3,4]

Although complications such as diverticulitis occur in the setting of obvious inflammation and infection in 1 or more diverticula, some limited evidence has suggested that a chronic state of low-grade mucosal inflammation may play a role in diverticulosis and contribute to the development of chronic gastrointestinal symptoms, also known as symptomatic uncomplicated diverticular disease (SUDD).[5] For example, alterations in the gut microbiota have been implicated in the pathogenesis of diverticulosis while diverticulosis-associated dysbiosis may contribute to chronic mucosal inflammation.[6] In earlier studies of patients with symptoms attributed to diverticulosis who underwent colonoscopy screening or surgery, chronic mucosal inflammation was documented in biopsy specimens from areas adjacent to diverticula.[7,8] A recent study from Italy reported that patients with diverticulosis had significantly increased colonic macrophages compared with controls, regardless of symtoms.[9] However, these prior investigations were limited by small sample size,[7–9] lack of meaningful controls,[7,8] or comparisons that did not account for potential confounders.[9] Therefore, high-quality evidence linking diverticulosis with subacute colonic inflammation remains an important prerequisite to identify potential inflammatory mechanisms that underlie the pathogenesis of diverticular disease and other chronic digestive disease symptoms.

Conflicts of interest

The authors disclose no conflicts

In this issue of *Clinical Gastroenterology and Hepatology*, Peery et al[10] addressed this knowledge gap in their report of an observational study of 619 outpatients undergoing a first-time screening colonoscopy. Patients reported by the endoscopist to have diverticulosis were defined as cases (41% of patients) and were compared with controls without diverticulosis. Biopsy specimens were taken from normal-appearing mucosa in the sigmoid colon for assessment of immune markers and messenger RNA (mRNA) gene expression of cytokines. Gastrointestinal symptoms were assessed using Rome III diagnostic criteria for irritable bowel syndrome (IBS). Contrary to the hypothesis, there was no association between diverticulosis and markers of subclinical colonic inflammation, including mRNA expression of tumor necrosis factor, CD4+ cells, CD8+ cells, or CD57+ cells. There was no association between diverticulosis and IBS or chronic abdominal pain. Furthermore, no mucosal inflammation was found among patients with symptoms and diverticulosis compared with those having IBS or abdominal pain without diverticulosis.

These data provide convincing evidence regarding the lack of a relationship between subclinical mucosal inflammation and colonic diverticulosis among individuals without a history of diverticulitis and overt diverticular inflammation. However, the results should be interpreted in the context of the cross-sectional nature of the study design. Although the analysis was derived from a prospective study designed to assess lifestyle risk factors for diverticulosis, the assessment of mucosal inflammation was performed at the same time as the colonoscopic diagnosis of diverticulosis, which was likely already present for years. Assessment of mucosal inflammation markers before the development of documented incident diverticulosis would have permitted greater inference regarding a potential causal role for low-grade mucosal inflammation in the etiology of diverticulosis and chronic gastrointestinal symptoms.

Although no associations were generally observed for most markers compared with individuals without diverticulosis, patients with diverticulosis had significantly lower levels of expression of interleukin 6 (IL6) and IL10 mRNA. IL10 is an important anti-inflammatory mediator and suppresses production of proinflammatory cytokines,[11] whereas IL6 plays both proinflammatory and anti-inflammatory roles in local and systemic inflammation.[12] Therefore, decreased levels of these mediators may predispose to increased mucosal cytokine production, contributing to a pattern of an unbalanced cytokine profile in a subclinical inflammatory state. Interestingly, several previous studies also reported lower mucosal mRNA expression of IL10 in patients with IBS compared with healthy controls.[13,14] These data leave open the possibility that mRNA expression of IL6 and IL10 may be possible biomarkers of local immune regulation of mucosal inflammation. Future studies will need to confirm these findings and determine how their expression may be related to diverticulosis.

A subset of patients with diverticulosis with a spectrum of gastrointestinal symptoms in the absence of macroscopically overt colitis or diverticulitis, classified as SUDD, may have a clinical diagnosis of IBS. Despite the potential overlap, evidence for the relationship between diverticulosis and gastrointestinal symptoms remains inconclusive. In a population-based, cross-sectional survey among 1712 participants, the presence of IBS was associated with increased odds of diverticulosis, but not diverticulitis, and the association was much

stronger in patients older than 65 years.[15] Similarly, a population-based Swedish study including 742 participants undergoing colonoscopy reported that diverticulosis was associated with abdominal pain and diarrhea-predominant IBS in participants older than 60 years. In another colonoscopy-based study in Japan, only distal, but not proximal, diverticulosis was associated with an increased risk of IBS. In contrast to these prior findings, results from the current study do not support a link between diverticulosis and chronic gastrointestinal syndromes. However, this analysis may be underpowered owing to the limited number of participants with IBS or abdominal pain. In addition, the predominant association found in prior studies for older individuals and those with distal diverticulosis highlights the potential that there remain important subgroups in which low-grade inflammation may predispose to development of gastrointestinal symptoms or SUDD.

What are the clinical implications of this study? The lack of low-grade inflammation underlying gastrointestinal symptoms secondary to diverticulosis questions the classification of SUDD as a clinically distinct patho-physiologic entity and the rationale for treating SUDD with the anti-inflammatory mesalamine. However, some,[16] but not all,[17] data from randomized controlled trials have shown some evidence for the beneficial effects of mesalamine in improving symptoms and inducing remission of SUDD. Furthermore, there remains the possibility that a subgroup of SUDD patients may have a potential subclinical inflammatory basis that may be uncovered by studies with larger populations or designed to specifically compare the inflammation status between SUDD patients and healthy individuals with neither symptoms nor diverticulosis.

In summary, Peery et al[10] did not find that diverticulosis was associated with most mucosal inflammatory markers or gastrointestinal syndromes. These results do not support the popular hypothesis that low-grade inflammation is either an etiologic factor or a consequence of chronic diverticular disease. Further evidence is clearly needed before considering routine use of anti-inflammatory agents for treating gastrointestinal symptoms in patients with diverticulosis.

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