Pathophysiology and prevention of diverticulitis and perforation

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ABSTRACT

Objective: This article gives an overview of the current evidence and theories in the pathophysiology of diverticulosis, diverticulitis and perforation and discusses its prevention.
Background: Diverticular disease is one of the most common diseases related to the gastrointestinal tract in Western countries. The pathogenesis of this disease process is probably multifactorial, but remains poorly understood and inadequately investigated.
Methods: A literature search was performed in order to give an overview of the current evidence and theories in the pathophysiology of diverticula formation and the factors related to progression towards inflammation and even perforation. Strategies for prevention of (perforated) diverticulitis are also discussed.
Results/conclusion: The pathogenesis of diverticular disease and its complications seems to be a result of a complex interaction between exposure to a low-fibre diet, possible genetic influences, the coexistence of other bowel diseases and the impact of medicine use. This eventually leads to alterations in colonic pressures and motility and structural changes of the colon wall. Unfortunately the evidence is frequently conflicting in the present literature or lacking altogether.

KEYWORDS

Pathophysiology diverticulitis, diverticular disease, prevention, perforation

INTRODUCTION

The prevalence of diverticulosis is estimated at 5% by the age of 40 years, up to 65% at 80 years of age.[1,2] Its exact prevalence is difficult to assess because most people remain asymptomatic.[2] Only 10 to 25% of patients with diverticulosis will manifest any related clinical symptoms.[2,3]

The pathogenesis of this disease process is probably multifactorial involving dietary habits, changes in colonic pressure, motility and wall structure associated with ageing.[4] The reason why a subgroup of individuals progresses from asymptomatic to symptomatic or even complicated diverticular disease remains poorly understood. This article gives an overview of the current evidence and theories in the pathophysiology of diverticulosis, diverticulitis and perforation and discusses its prevention.

PATHOPHYSIOLOGY DIVERTICULA OF THE COLON

In Western nations diverticula are most common in the left colon. This is in contrast to Asian nations where they occur primarily in the right colon.[5] This difference suggests a role for genetic, environmental or lifestyle factors in the aetiology of diverticular disease.[6]

Diverticula are most notable in the left colon, with up to 99% having some degree of sigmoid involvement.[7] They protrude most commonly in four rows between the antimesenteric and mesenteric taenia.[8] The majority of diverticula pass through the bowel at weak points in the circular muscle layer where the blood vessels penetrate it to supply the mucosa.[8,9] This suggests that intraluminal pressure might play a role in their formation. These pulsion diverticula are in fact 'false' diverticula as not all layers of the bowel wall are involved.[4]

The maintenance of the colonic wall is provided by extracellular matrix, with components such as collagen and elastin.[10] The mechanical characteristics of the bowel

are maintained via circular and longitudinal muscle layers. The circular muscle thickens in regular bands of contraction (plicae circulares) which control peristalsis. The longitudinal muscle also condenses in thick bands (taeniae coli) which serve to pull the colon to a relatively short functional length. Thickening of the muscular layer is one of the most consistent features of diverticulosis.[7]

Accumulation and aberrant deposition of connective tissue fibres (elastin and collagen) underlie the altered muscle morphology.[11] The muscle cells themselves do not change, but the taeniae become thickened secondary to elastin depositions, which leads to contraction in this layer and thickening of the circular muscle layer.[11-13] This narrows the lumen. In addition, systematic contractions of the circular muscle divide the bowel into a series of compartments. Altogether these colonic wall changes lead to an increase in intracolonic pressures.[14-16]

Elastin depositions and cross-linking of collagen continue throughout life in all layers of the colonic wall.[17] Increased elastin deposition may result from intermittently increased colonic pressure, which in turn is due to reduced faecal load produced by a Western low-fibre diet. Together with a decrease in tensile strength of the colonic wall, caused by an increase in cross-linking of collagen fibres with age and caused by a low-fibre diet as well, these changes in muscle morphology will result in weakening of wall resistance.[13,18-20] The increased depositions of these two connective tissue fibres (elastin and collagen III) are observed to be more pronounced in diverticular disease.[21,22] It is thought that a disruption of the balance between matrix metalloproteinases (MMPs) and their inhibitors (TIMPs) may be involved in the pathogenesis of diverticular disease, through remodelling of the colonic extracellular matrix, particularly collagen.[10] An overexpression of TIMPs in the muscular layer affects the turnover of extracellular matrix, resulting in the formation of diverticula and their complications.[7,10,22] An increased synthesis of type III collagen is observed in diverticulosis, but its significance remains to be elucidated.[21] The disturbance of the collagen texture (lower ratio of mature collagen type I and immature collagen type III) is thought to weaken the bowel wall, hence leading to the onset of diverticula.

Besides colonic wall changes, disordered motility has also been suggested as a cause of increased intraluminal pressure and hence as a pathogenetic factor in diverticulosis.[23] Colonic motility is influenced by the ageing process of its smooth muscle, causing an increase in segmental contractile activity.[24] Patients with symptomatic diverticular disease have shown to have higher motility indices than asymptomatic patients or healthy persons.[23] Nevertheless, absolute evidence is still lacking, since most studies on colonic motility and myoelectrical activity were biased by poor patient selection, heterogeneity of clinical conditions, recording techniques, and duration of the recording and mostly based on small numbers of patients.[23]

Neurophysiopathological data to support the increased colonic motility are sparse in the present literature. The high intracolonic pressure might be related to an imbalance in usual excitatory and inhibitory neural influences (increased cholinergic stimulation). Cholinergic nerves were dominantly present in the diverticular colon compared with controls.[25,26] Moreover, patients with diverticular disease have shown substantial structural alterations of the enteric nervous system mainly characterised by a significant lower number of glial cells and a lower number of interstitial cells of Cajal in the mesenteric plexus and within the muscle.[27] These cells are emerging as potential colonic pacemaker cells, and their loss might explain intestinal motor abnormalities reported in diverticular disease.

The influence of Western diet habits (red meat, low fibre) on the evolution of diverticular disease has been well established.[1,28,29] These dietary factors lead to increased colonic transit times, smaller stool volumes and subsequently to raised intracolonic pressures, all of which may contribute to the development of diverticulosis.[30] An increase in diverticular disease in developing countries has been documented, concurrent with the adoption of Westernised dietary habits.[4] An unexplained curiosity in the increase in diverticular disease in Asia is that it is mostly right sided, which suggests a genetic component in the development of diverticulosis.[31]

Some genetic disorders have been associated with a strong predisposition towards diverticula formation. Most of these syndromes are associated with a connective tissue disorder (Ehler-Danlos, polycystic kidney disease).[6] But literature is conflicting about this matter.[32] The same is thought about Saint's triad (the aggregation of gallstones, diverticulosis of the colon and hiatus hernia in elderly people). Connective tissue abnormalities causing herniosis might be the causing factor in this triad, although fibre-depleted diets may also be causatively related to Saint's triad.[33]

Recent studies show increasing mitochondrial dysfunction in the ageing colonic epithelia and this correlates well with diverticular disease prevalence.[34] It remains unclear whether these findings play a role in pathogenesis or are simply related to ageing.

It has been suggested that the irritable bowel syndrome may be an early stage in the development of diverticulosis.[35,36] Although a lack of dietary fibre and higher colonic motility activities caused by changes in the enteric nervous system have been implicated as aetiological factors in both conditions, available evidence supporting this theory is conflicting in the present literature. As both conditions are relatively common, the likelihood of coincidental occurrence in the same individual is

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quite high.[37] It is therefore almost impossible to predict which patients are symptomatic as a direct result of their diverticulosis. In the same manner, persistence of symptoms after surgical resection for symptomatic diverticular disease can be explained.[37]

In conclusion, the evidence from studies in man suggests a relationship between diet/lifestyle and diverticular disease, but there remains a lack of robust definitive evidence.

PATHOPHYSIOLOGY OF DIVERTICULITIS

It is estimated that 10 to 25% of patients with diverticulosis will experience inflammation at some point during their lives.[38] Like the pathophysiology of diverticula, the aetiology of diverticular inflammation is also speculative. Development of diverticulitis has been described similarly to that of appendicitis. Diverticula may become acutely inflamed through impacted faeces, leading to an obstruction of the lumen, raising intradiverticular pressure by continuing mucus formation and ultimately causing ulceration within the diverticular mucosa.[39] This event then allows for proliferation of bacteria, diverticula distension, and localised ischaemia. Eventually, perforation of variable extent may result, accounting for a range of symptoms.[40,41] It is possible that the increased colonic pressure in diverticular disease is also responsible for pushing fecaliths into the diverticula.

Dietary shifts during the past century have likely not only influenced colonic motility, but also altered colonic flora.[42] The colonic environment has likely undergone radical changes in the past century due to decreases in both soluble and insoluble fibre. Higher levels of *Bacteroides* and lower levels of *Bifidobacteria* have been found in studies comparing gut flora between Westernised and rural populations. This change in colonic microbial environment may be an important element in the transformation of asymptomatic diverticular disease into diverticulitis, but its exact role has not been adequately defined.[43]

In addition to the 'typical' form of diverticulitis, it is increasingly recognised that luminal mucosal inflammation may coexist with diverticula.[44,45] This low-grade inflammation shares histological features with inflammatory bowel disease. The pathogenesis of this so-called diverticular colitis, sigmoiditis, or segmental colitis is unknown, as is its relationship with inflammatory bowel disease.[45,46] Nevertheless, low-grade diverticular colitis might be the reason why some patients are chronically symptomatic. This phenomenon has been described before in inflammatory bowel disease, where colonic symptoms may persist after resolution of inflammation.[47] The acute diverticular inflammation may have provoked an alteration in colonic neuromuscular function and may be responsible for chronic symptoms, even in the absence of inflammation.

PATHOPHYSIOLOGY OF PERFORATED DIVERTICULITIS

Although diverticulosis is common, complications requiring surgery occur in only approximately 1% of patients with the disease.[48] The incidence of diverticular perforation has been estimated at 4/100,000 population per annum.[49] About 80% of patients presenting with perforated diverticulitis do not have a previous history of diverticular disease.[49]

The natural history of complicated diverticulitis remains poorly understood, probably because consultant surgeons see only two to three cases a year and almost a third of patients die from unrelated causes during follow-up.[50] In case of perforated diverticulitis this percentage might be even higher, up to 50% within five years.[51]

The aetiology of perforation remains unknown, but as stated before, it is thought to be a result of excessive rise in intradiverticular pressure and focal necrosis.[52] This local perforation may form pericolic phlegmones and pus collections (Hinchey I).[53] If this process progresses, localised abscesses may be formed between loops of small bowel or in the pelvic peritoneum (Hinchey II). If the pus cannot be contained, the abdominal peritoneum gets contaminated producing generalised purulent peritonitis (Hinchey III). The same is found when a large intraperitoneal diverticular abscess ruptures into the abdominal cavity.[54] If the initial perforation is large, faecal contamination of the abdominal cavity can occur (Hinchey IV).[53]

Patients with diverticular disease in general show raised intracolonic pressures, especially in the sigmoid colon.[14] As almost all diverticular perforations occur in the sigmoid colon, these pressure changes must be an important aetiological factor. Besides that, the properties of the colonic wall are likely important, because diverticula consist predominantly of mucosa, lacking a smooth muscle layer. The mucosal barrier is vulnerable and may be impaired by various exogenous factors.[55]

NSAIDs have been implicated as a risk factor for perforation in diverticulitis.[49,56-58] NSAIDs inhibit the cyclo-oxygenase enzyme and cause topical mucosal damage, increasing colonic permeability. Besides, they reduce prostaglandin synthesis, which is important in maintaining an effective mucosal barrier.[59]

Corticosteroids and opiate analgesics are also related to an increased perforation rate.[60,61] Corticosteroids have strong immunosuppressive and anti-inflammatory effects, which may result in an impaired ability to contain the perforation initially.[57] This will lead to more severe

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inflammatory complications. Besides, symptoms and signs in the immunosuppressed patient may well be masked, often delaying and underestimating diagnosis and its severity.[62,63] The prevalence of diverticulosis in immunosuppressed patients may not differ from that in the rest of the population, but there is undoubtedly a much higher incidence of complicated diverticulitis in such patients.[63] Opiates slow intestinal transit and raise intracolonic pressures.[61] By slowing transit time, the diverticular mucosa may have a prolonged exposure to potentially damaging pathogens, such as bacteria.

Unfortunately the causal relationship between these drugs and perforated diverticulitis is mainly based on (small) case series or case-control studies. Hard evidence is lacking in the present literature. Besides, if these drugs are a true risk factor for perforation, they would account for less than 20% of cases: other risk factors must be important.[54]

The role of smoking and alcohol intake in perforated diverticulitis is also unknown. Nicotine might predispose to diverticular inflammatory complication by reducing mucosal immunity,[64,65] but hard evidence is lacking in the present literature.[66]

Since the incidence of diverticulosis increases with age, the majority of patients presenting with symptoms are the elderly. Complicated diverticulitis is also observed predominantly in older patients. This problem is caused by an unusual presentation of diverticular complications in the elderly patient, with consequent delay in diagnosis. Polypharmacy may further exacerbate this problem and may even increase the risk of developing complications (NSAIDs, corticosteroids).[67] The relatively high incidence of comorbidities in the elderly and the unusual presentation of the disease will lead to a very high morbidity and mortality rate for this group of patients.[51]

On the other hand, complicated (perforated) diverticulitis is relatively frequently seen in younger (male) patients.[68] Although diverticulitis is uncommon in patients less than 40 years old, accounting for only 5% of all patients admitted for diverticulitis, it has been thought to be a more virulent condition in this age group.[69,70] But again the present literature is conflicting. Several recent publications have suggested that the disease is not more virulent in the younger patients.[71-73] The high rate of complications and perforations may be attributed to a high misdiagnosis rate because diverticulitis may not be suspected in younger patients with abdominal complaints.[74,75]

PREVENTION OF DIVERTICULITIS AND PERFORATION

The possible role of diet and lifestyle offers strategies for prevention. Large prospective studies have identified a preventive effect of both vegetable and high fibre intake and physical exercise in the development of diverticular disease, as well as diverticulitis.[76-78] The protective action of dietary fibre would make the stools bulkier, thereby increasing the colon size and decreasing intraluminal pressures, and reducing colonic transit time.[79,80] Fibre as a dietary supplement may be beneficial in prevention. It is nevertheless remarkable that the incidence of diverticular disease has not been found to be reduced, while several studies have shown an increased intake of fibres in Western populations over the last three decades.[81] The exact role of fibres in the pathophysiology of diverticulosis and its prevention remains unclear. And when symptoms have developed, evidence of a benefit of fibre is even less convincing.[81]

A reduction in transit time was the consistent finding in most of the studies that addressed the effect of physical exercise on colonic function. An increase in colonic motor activity has been postulated; however, the exact mechanism of this effect is still not clear.[78]

As mentioned above, patients with symptomatic diverticular disease have shown to have higher motility indices than asymptomatic patients or healthy persons.[82] This suggests that anticholinergic or antispasmodic drugs might improve symptoms by diminishing muscular contractions. Nonetheless, there is no evidence to support this in the present literature.[40]

One of the latest therapies for the prevention of recurrent diverticulitis is the use of mesalazine, rifaximin or a combination of both.[83,84] The rationale for this is that mesalazine inhibits some key factors of the inflammatory cascade.[85] The protective role of mesalazine in the recurrence of symptomatic diverticular disease is thought to be similar to that for the use in chronic inflammatory bowel disease.[85,86]

Another very recent therapy is the use of probiotics.[87] Probiotics diminish changes in the spectrum of intestinal microflora and the adherence and translocation of pathogens. They also regulate production of antimicrobials and interact as competitive metabolites with pro-inflammatory organisms. Especially the combination of *Lactobacilli* spp. with rifaximin seems effective in reducing severe forms of diverticulitis and the prevention of recurrences, hence reducing surgical treatment significantly.[88,89]

The role of surgery in the prevention of (complicated) diverticular disease is unclear. Formally, elective sigmoid resection was recommended after two episodes of uncomplicated diverticulitis to prevent serious complications of recurrent colonic diverticulitis.[90] This guideline was based on the assumption that recurrent episodes of diverticulitis will lead to more complications and higher mortality. The data to support this assumption are based on small and older studies. Advances in diagnostic modalities, medical therapy, and surgical techniques over the past two decades have changed both the management and outcomes of diverticulitis.[91]

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Patients treated nonoperatively would be expected to do well without elective colectomy, since most patients will not have further episodes of diverticulitis.[92,93] Recurrent episodes of diverticulitis do not lead to more complications and more conservative treatment failure.[94,95] At present it is thought that elective resection for uncomplicated diverticulitis does not alter outcome, nor does it decrease mortality or prevent severe complications of the disease such as perforation.[96,97] For approximately 80% of the patients perforation is the first manifestation of diverticular disease.[49]

Finally an association between the use of calcium channel antagonists and perforated colonic diverticular disease was demonstrated.[98] Calcium channel antagonists, which reduce colonic contractility and tone, protected against perforation. Further studies are required to confirm this association, but it may represent a potentially useful preventive therapy.

CONCLUSION

Although diverticular disease is one of the most common diseases related to the gastrointestinal tract in Western countries its pathophysiology remains poorly understood and inadequately investigated. Much of the evidence suggests that the pathogenesis of diverticular disease is a result from a lifelong exposure to a low-fibre diet, leading to alterations in colonic pressures and motility and colon wall structural changes. Unfortunately the 'evidence' is frequently conflicting in the present literature or lacking altogether. This complex interaction between colonic structure, motility and diet, the possible genetic influences, the coexistence of other bowel diseases and the impact of medicine use, makes it difficult to investigate. It may even be so that clinical subtypes of diverticular disease exist in terms of pathophysiology and symptomatology requiring different treatment strategies. Further basic and clinical investigations need to be done to fill up the several gaps in the knowledge of pathophysiology of diverticulosis and diverticulitis and its treatment and prevention. For the same reason, there is a need for further good quality epidemiological research to identify risk factors in diverticular perforation. Whether new insights into the aetiology will lead to new surgical strategies for prevention and treatment of perforated diverticulitis remains to be seen.

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