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Review

Diverticular Disease: A Review on Pathophysiology and Recent Evidence

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Keywords: Diverticular disease, Diverticulitis, SCAD, diet

ABSTRACT

Diverticular disease is common condition globally, especially in Western countries. Diverticulitis, Symptomatic uncomplicated Diverticular disease and Segmental Colitis associated with diverticula constitute diverticular disease. Although most patients with diverticula are asymptomatic, around 25% of patients will experience symptoms whilst 5% of patients have an episode of acute diverticulitis.

The prevalence increases with age with more than one theory being put forward to explain its pathogenesis. Faecolith entrapment in diverticula results in colonic mucosal damage and oedema, bacterial proliferation and toxin accumulation leading to perforation. This mechanism may explain diverticulitis in elderly patients with multiple, larger diverticula. Ischaemic damage could be the cause of acute diverticulitis in younger patients with sparse diverticula where more frequent and forceful muscular contractions in response to colonic stimuli occlude the vasculature leading to ischaemia and microperforation.

Chronic colonic active inflammation in the presence of diverticular disease is termed Segmental colitis associated with diverticulosis. Its pathophysiology is still indeterminate but together with its clinical picture, may mimic Inflammatory Bowel Disease. Treatment includes a high fibre diet together with antibiotics and/or salicylates with surgery in severe cases.

Indications for elective surgery in diverticular disease have changed over the past decades as this may not suggest a reduction in morbidity and mortality. Prophylaxis with probiotics, laxatives, anti-spasmotics, anticholinergic drugs and salicylates are at the centre of recent studies. Studies are also challenging previously believed facts regarding dietary fibre, nuts and seeds whilst emphasizing the effect of healthy lifestyle and smoking on the increasing incidence of DD.

Key words: Trauma, Ischaemia, Segmental Colitis associated with diverticula, Surgery, Prophylaxis.

1. Introduction

Diverticular disease is a common condition in the Western world and is defined as clinically significant and symptomatic diverticulosis due to Diverticulitis, uncomplicated Diverticular disease (DD) and Segmental Colitis associated with diverticula.[1] It is present in around 10% of people aged less than 40 years and increases up to more than 70% in people aged more than 80 years, with prevalence being similar in both men and women. [2] Around 25% of people with diverticula will experience an episode of symptomatic DD. [3]

Diverticulitis may be sub-classified as complicated or uncomplicated, with the former comprising fistulas, abscesses, obstruction and perforation (Figure 1).[1]

Historically, inflammation leading to diverticulitis was thought to be due to a primary infection of the diverticular task. However, no pathogens were actually found to cause diverticulitis. Because of this, the combination of broad spectrum antibiotics together with metronidazole was the mainstay of treatment for an acute episode. More recently, 2 main theories have been recognized as hypothesis for the pathogenesis of diverticulitis.[4]

2. Pathophysiology

The pathophysiology of DD is not completely understood. Many factors have been thought to contribute to its pathogenesis including colonic wall structure, colonic motility, diet and fibre intake, obesity and physical activity as well as genetic predisposition. [1,3]

"TRAUMATIC THEORY"

The most accepted current theory that describes the underlying mechanism in acute diverticulitis is "traumatic" damage to the diverticulum and subsequently bacterial proliferation. Increased pressure within the colon leads to faecoliths present within the lumen being pushed into the diverticuli, especially larger ones, resulting in stool impaction in the diverticular task. The entrapped faecolith causes trauma by abrading the mucosa of the diverticular sac leading to local inflammation and bacterial overgrowth. If the proliferating bacteria breach the mucosal wall to involve the full bowel wall, their toxic and gas production may eventually lead to bowel perforation. Furthermore, the irritation and inflammation caused by trapped faecoliths lead to vascular congestion and oedema, which in turn cause further obstruction, with secretions from

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the proliferating bacteria accumulating in the diverticular sac, thus increasing the risk of perforation (Figure 2). This theory could well describe the sequence of events leading to acute diverticulitis in older patients with larger diverticula, and since bacterial overgrowth is the most important pathological factor, antibiotics are the basis of treatment.[4]

"ISCHAEMIC THEORY"

In younger patients, where the finding of colonic diverticula may be sparse, acute diverticulitis may be the result of ischaemic damage. Studies have demonstrated neuromuscular differences in the affected colonic areas leading to more prolonged and forceful contractile impulses.[4] The activity of choline acetyltransferase was shown to be lower in circular muscle of patients with DD, whilst there was an increase in the number of M3 receptors. Furthermore, patients with DD showed increased sensitivity when administered exogenous acetylcholine, when compared to controls.[5] All these factors lead to increased sensitivity to cholinergic denervation leading to excessive contractile impulses in response to normal stimuli in the diverticular wall.[4] The "ischaemic" theory suggests that long-standing contractile impulses of the colon cause persistent compression of blood vessels at the diverticular neck. The neck is found in the colonic circular muscular muscle wall, which may be compressed by muscular spasm, triggering ischaemia at the mucosa and micro-perforation (Figure 2). This theory therefore puts forward another possible mechanism for the pathophysiology of acute diverticulitis where faecal entrapment is unlikely and the role of bacteria is not so prominent. Treatment with antibiotics is used more as prophylaxis against opportunistic infections on the damaged colonic mucosa rather than to treat the primary infection itself.[4] In fact, The American Gastroenterology Association (AGA) suggest that 'antibiotics should be used selectively, rather than routinely, in patients with acute uncomplicated diverticulitis'.[6]

Whenever abdominal pain is present in patients without the acute symptoms of diverticulitis, this is defined as symptomatic uncomplicated diverticular disease (SUDD). [1] Interestingly, 22% of patients with SUDD describe left lower quadrant pain lasting more than 24hours. This could be produced by the sustained spastic state of the bowel wall which predisposes to mucosal ischaemia in the diverticulum. [4] Clemens et al studied the underlying mechanisms which may be implicated in SUDD and it was found that such patients have hypersensitivity in the sigmoid colon bearing diverticula, which is similar to the pathophysiology in irritable bowel syndrome (IBS). More studies on the two diseases are required in order to be able to confirm whether patients suffering from IBS are more likely to have diverticulosis and hence be identified as SUDD in view of the chronic abdominal pain.[7]

SEGMENTAL COLITIS ASSOCIATED WITH DIVERTICULOSIS (SCAD)

DD, with its underlying inflammatory process, may closely mimic inflammatory bowel disease (IBD). Segmental colitis associated with diverticulosis (SCAD), or Diverticular colitis, is nowadays recognized as an independent entity. It describes areas of the colon affected with DD which demonstrate chronic active inflammation, irrespective of diverticular inflammation. Symptoms usually consist of diarrhoea, abdominal cramps and fresh/altered rectal bleeding.

The exact pathogenesis of SCAD remains unclear, but it is most likely to be multifactorial (Figure 2).[8]

In contrast to IBD, it is believed that SCAD runs a more benign and self-limiting course with patients achieving remission without treatment and recurrence. Management includes a high fibre diet in combination with antibiotics and/or salicylates. As suggested by Rampton, a 7 day course of Ciprofloxacin 500mg BD together with Metronidazole 500mg TDS may be used to treat patients with SCAD. Furthermore, 2.4g-3.2g of Mesalazine may be added daily in cases of incomplete response to antibiotics or recurrent symptoms. [8] An alternative antibiotic regime used in patients who are unable to tolerate Ciprofloxacin and Metronidazole is an Ampicillin-based antibiotic regime.[9]

Recently, Tursi et al have demonstrated how acute mild to moderate diverticular colitis can be treated with a combination of beclomethasone dipropionate (BDP) and the probiotic VSL#3, as shown in Table 1. The probiotic was administered for a total of 15 consecutive days whilst BDP for 4 weeks with the great majority of patients achieving symptomatic remission by week four. Immunosuppressants, such as systemic steroids, may be used in severe cases as 3rd line agents. Steroid-dependent or steroid-refractory cases may then require surgical interventions, with decisions being taken according to each individual case.[8] Table 1 summarises the management algorithm for patients with SCAD.

3. The Role of Surgery

In the past, patients with recurrent episodes of diverticulitis generally underwent elective surgery after the second acute episode. [3] This was based on the fact that there was thought to be an increased risk of complications and reduction in response to treatment after the second acute episode. Recently however data shows that the indication for elective surgery should not be based on the number of acute episodes alone, but should take into consideration the patients' risk factors, age, comorbidities, severity of the episodes and any complications. One major benefit with respect to elective surgery is the removal of symptoms that are experienced with acute diverticulitis. However this does not guarantee a reduced risk of emergency surgery or colostomy, reduction in septic complications of acute diverticulitis or a general reduction in morbidity and mortality.[10] Therefore, the decision for surgical intervention should be based on the benefits and risk exposure to each individual patient, once the patient has recovered from an episode of acute diverticulitis.

4. Prevention of Diverticulitis

DRUGS

Studies and advances in medical treatment have demonstrated that a number of drugs may be used in the prophylaxis of DD and therefore further reducing the need for surgery. Laxatives prevent constipation by reducing faecolith formation and the risk of traumatic damage to the diverticulum by stool impaction. Conversely, the administration of spasmolytics in patients with abdominal pain lasting more than 24 hours interrupts the colonic contractions and relieves the ischaemic injury. Anticholinergic drugs also reduce the contractions in colonic circular muscle hence reducing vascular ischaemia. [4] Interestingly, aminosalicylates particularly Mesalazine have been used as maintenance of remission in patients with diverticulitis. In a study by Rampton, a maintenance dose of Mesalazine 1.6g daily was administered to patients with the addition of probiotic VSL#3 in patients with more severe disease to maintain remission (Table 1).[8]

Although Mesalazine is used in patients with ulcerative colitis, there is no clear evidence that Mesalazine alone reduces the symptoms of DD.[11] There is also no clear evidence that Mesalazine reduces the risk of acute episodes of diverticulitis and, in fact, the AGA advices against the use of Mesalazine after an acute episode of uncomplicated diverticulitis.[6,11] Similarly current guidance suggests that probiotics are effective in reducing symptoms is lacking. Several studies have been conducted aiming at evaluating the clinical efficacy of probiotics. However, no definitive results have yet been achieved, mainly due to the diversity of the available studies.[12]

5. Recent Evidence

Multiple factors have been identified as risk factors for DD and its complications, which are amongst the most common gastroenterological indication for hospitalisation. Amongst the major risk factors there are aging and lifestyle diverticulitis and diverticular bleeding. Physical activity, obesity, diet (including fibre content and nut, corn and popcorn consumption), smoking status are being analysed for their impact on disease symptomatology.[11]

5.1 Physical activity

Physical activity has been shown to reduce the risk of diverticulitis by 25%.[13] In a study by Strate et al where physical activity and DD were followed-up over 18 years, it was demonstrated that men performing the most vigorous activity had a 25% reduction of risk of diverticulitis in addition to a 46% risk reduction in diverticular bleeding when compared to men who exercised less.[14] Various mechanisms may describe this risk reduction including reducing intracolonic pressure, reducing colonic transit time and neuroendocrine alterations.[13] In fact, current guidance advises patients diagnosed with DD to engage in vigorous physical activity.[6]

5.2 Fibre intake in an Asymptomatic Patient

The theory that lack of dietary fibre is associated with an increased risk of diverticulosis has always been popular. [1] Painter and Burkitt had put forward that dietary fibre deficiency results in high colonic pressure in view of constipation that in turn results in mucosal herniation [15]. Their studies however have not proven that elevated intracolonic pressures are present in patients with diverticulosis and more recent studies are further confirming this.[16] Studies are suggesting that a high fibre diet may not protect against the development of diverticulosis, but it may protect against DD. In a small study, patients who on average consumed less fibre (21.4 g/day vs 41.5 g/day; $p<0.001$) were more likely to have DD. This study has been challenged by 2 studies by where both studies did not find an association between fibre intake and DD.[11] However, limitations to these studies are : the study by Song et al was performed in Asia, where in contrast to that in Western populations, colonic diverticula are more frequently found on the right side of the colon and the pathophysiology is different to that in Western populations[17]. In the other study by Peery et al, who carried out a short-term investigation of dietary habits before colonoscopy, failed to identify clear-cut pathogenetic elements.[18]

Data with regards to diet and DD originated from the European Prospective Investigation into Cancer and Nutrition (EPIC) Oxford study, where 47,033 healthy individuals were followed-up for 5 years and the risk of hospitalization secondary to DD was evaluated. Crowe et al found a reduced risk of DD complications, including a lower hospitalization risk and lower risk of death from DD with increased intake of fibre (25.5 g/day in women and 26.1 g/day in men), with a relative risk of 0.58 (95% CI 0.46–0.73) when compared to those with the low intake of fibre (<14 g/day).[19]

Similarly Aldoori et al analysed data from a prospective cohort of 47,888 US men over 4 years. It was found that there was an inverse relationship between the risk of DD and total dietary fibre intake after adjusting for age, energy-adjusted total fat intake and physical activity. This was mostly attributed to fruit and vegetable fibre. The relative risk for men on a low-fibre, high-total-fat diet was 2.35 (95% CI 1.38, 3.98) compared with those on a high-fibre, low-total-fat diet whilst the relative risk for men on a low-fibre, high-red-meat diet was 3.32 (95% CI 1.46, 7.53) compared with those on a high-fibre, low-red-meat diet.[20] Similar results were obtained in a retrospective study of 56 patients admitted with SUDD, where those with a high fibre intake (>25 g/day) had a reduced risk of symptoms (19% vs 44%) and diverticular complications (6.5% vs 32%).[21]

5.3 Fibre Intake in a Patient with a History of Acute Diverticulitis

Though current guidance suggests that a fibre-rich diet or fibre supplementation in patients with a history of acute diverticulitis, this is a conditional recommendation with very low quality of evidence.[6] In fact, there are no studies that

address whether dietary or supplemental fibre intake reduces the risk of recurrent acute diverticulitis. The benefits of fibre for chronic abdominal pain in patients with diverticulosis are inconsistent and do not necessarily imply benefit in terms of recurrent diverticulitis. A differential benefit of dietary fibre intake compared with fibre supplementation is unknown, as is the optimal daily dose of fibre necessary to achieve benefit. The benefit of fibre in patients with recurrent or complicated diverticulitis is also undefined.

There are controversial results in terms of symptom relief from fibre supplementation alone.[11] A meta-analysis analysed the therapeutic effect of fibre supplements and it was noted that there is minimal high-quality evidence for a high-fibre diet in the treatment of DD, and that most suggestions are based on inconsistent level 2 and mostly level 3 evidence. It is important to note that in this meta-analysis, one randomized controlled trial documented an improvement in clinical symptoms and a marked reduction in pain, whilst another documented only a reduction in constipation without a positive effect on symptoms with fibre supplementation.[22]

Type of fibre is also regularly discussed. Studies were performed to analyze the type of fibre supplements that relieve symptoms. In one study, administration of bran or ispaghula husk over 16 weeks or methylcellulose administration over three months did not result in less symptoms when compared to placebo. Similarly, 12 weeks of lactulose supplementation was no more effective than high fibre.[11] Thus, methylcellulose and lactulose are not effective in reducing symptoms.

Rifaximin in addition to fibre has shown to reduce more symptoms than administration of fibre alone. Rifaximin is a non-systemic antibiotic with a vast antibacterial action covering multiple organisms including gram-positive, gram-negative, aerobe and anaerobes. It is almost not-absorbed so its bioavailability within the gastrointestinal tract is relatively high.[11] In a meta-analysis assessing Rifaximin and fibre treatment, the pooled risk difference (RD) for symptom relief was 29.0% (rifaximin versus control; 95% CI 24.5–33.6%; $p<0.0001$) and the number needed to treat (NNT) was 3. Rifaximin in addition to fibre was also more effective in preventing acute diverticulitis than fibre alone, albeit with a low therapeutic advantage. The pooled RD in the treatment group was –2% (95% CI –3.4 to –0.6%; $p=0.0057$) and the NNT was 50.[23] Recently, a multi-centre, randomised, open trial analysed the result of administration of Rifaximin in addition to a high fibre regimen in secondary prevention of acute diverticulitis.

Recurrence of acute diverticulitis occurred in 10.4% of patients given Rifaximin together with fibre experienced in comparison to 19.3% of patients who received fibre alone ($p=0.033$).[24]

5.4 Smoking

Smoking is a well-known risk factors for diverticulitis, in a dose-response relationship.[13] In a Swedish mammography cohort, 36,000 females were followed-up from 1997 – 2008. It was found that the risk of hospital admission from DD was increased by 24% when compared to non-smokers. No significant dose-response relationship was demonstrated in this study. Furthermore, in a Swedish cohort study of 7500 men over 28 years, it was found that patients smoking during the period of study had a relative risk of 1.89 (95% CI 1.15–3.10) for perforated DD when compared to people who do not smoke.[11] In the EPIC-Oxford cohort, there was a relative risk of 1.34 in people who smoked less than 15 cigarettes per day and a relative risk of 1.86 in people who smoked 15 or more cigarettes per day of hospitalization for diverticular disease when compared to non-smokers.[19]

5.5 Body Mass Index (BMI)

An increasing problem is obesity which has been shown to increase the risk of diverticulitis by up to 80%.[13] Associations between acute diverticulitis and waist circumference, waist-to-hip ratio and body mass index have been identified.[1] The pathogenesis of these associations is still unclear however the difference in microbiology of the gastrointestinal tract observed in obese patients is currently being studied as a possible link to increased risk of diverticular disease, together with the fact that cytokines secreted from adipose tissue might play a role in the inflammatory process of diverticulitis. [25]

A cohort study by Rosemar et al recruited 7500 men in Sweden and these were followed-up for 28 years. This study found a x4 fold increased risk of diverticulitis in men with a BMI of more than 30, when compared to men with BMI of 20-22.5.[26] Strate et al also demonstrated this relationship when 47,000 men were followed-up for 18 years; there was a 78% increased risk of diverticulitis in males with BMI of more than 30 as well as a x3 times greater risk of diverticular bleeding when compared to men with BMI <21.[27]

5.6 Non-Steroidal anti-inflammatory drugs

Another identified risk factor for complicated DD is the use of nonsteroidal anti-inflammatory drugs (NSAIDs).[1] The regular use of such drugs was found to increase the risk of an initial episode of acute diverticulitis by 70%, whilst regular aspirin use by 25%.[13] Furthermore, a large meta-analysis has demonstrated a significantly raised risk of diverticular bleeding, perforation and abscess formation in patients with NSAID use when compared to nonusers.[28] Because of this, the AGA advises patients to avoid the use of non-aspirin NSAIDs in case of a history of diverticulitis, albeit with a very low level of evidence.[6]

5.7 Nuts, seeds and Corn

A subject which is increasingly being challenged recently is the result of nuts, seeds and corn intake on the prevalence of DD. For decades, patients with DD were advised to avoid foods such as nuts, corns and seeds. This was based on the

hypothesis that these particles might obstruct a narrow-necked diverticulum leading to a cascade of events similar to that of the "traumatic" theory. In a landmark study by Strate, a prospective cohort of 47,228 male health professionals were evaluated for administration of dietary nuts, corn and seeds for 18 years. Results showed that there was no increased risk of complicated diverticulitis and no significant relationship with diverticular bleeding. Instead, consumption of these types of food may inversely be protective against diverticulitis.[29] Hence, the idea that consumption of these foods is a risk factor for diverticular disease is not proven and suggestions to avoid nuts, seeds and corn should be re-evaluated.

6. Conclusion

Although the "traumatic and ischaemic" theories describe different mechanisms as to the pathophysiology of diverticulitis, both may act in the same patient and both act differently amongst different patients. Lifestyle practices especially physical activity, obesity, smoking and NSAID use play a very important role in the incidence of diverticulitis and more research is concentrating on this. Research is also questioning knowledge that was believed for a long time pertaining to dietary practices and is continuously revealing new facts to help understand risk factors and pathophysiology related to DD.

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