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Review

Epidemiology and risk factors for diverticular disease

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Summary. Diverticulosis of the colon is the most frequent anatomical alteration diagnosed at colonoscopy. The prevalence of the disease is higher in elderly patients over 65 years old, recent studies show an increment also in youngers over 40 years old. Even its large prevalence in the population, its pathophysiology still remain poorly understood. It's widely accepted that diverticula are likely to be the result of complex interactions among genetic factors, alteration of colonic motility, lifestyle conditions such as smoking, obesity, alcohol consumption, fiber and meat intake with diet. Recently many authors considered also alterations in colonic microbiota composition, co-morbidity with diabetes and hypertension and the chronic assumption of certain medications like PPI, ARB and aspirin, as important risk factors for the development of diverticulosis. The aim of this narrative review is to summarise current knowledges on this topic. (www.actabiomedica.it)

Key words: diverticulosis, diverticular disease, risk factors, epidemiology

Introduction

Diverticulosis of the colon is an anatomic alteration of the colonic wall characterized by the presence of pockets (called diverticula) which occur when colonic mucosa and sub-mucosa herniate through defects in the muscle layer of the colon wall (1). Diverticulosis is merely the presence of colonic diverticula; these may, or may not, be symptomatic or complicated. 'Diverticular disease' is defined as clinically significant and symptomatic diverticulosis; this may be from true diverticulitis or from other less well-understood manifestations (e.g. visceral hypersensitivity in the absence of verifiable inflammation) (2). The overarching term 'diverticular disease' implies that the pathologic lesion (diverticulosis) rises to the level of an illness. Symptomatic Uncomplicated Diverticular Disease (SUDD) is a subtype of DD in which there are persistent abdominal symptoms attributed to diverticula in the absence of macroscopically overt colitis or diverticulitis. In contrast, 'diverticulitis' is the macroscopic inflammation of diverticula with related acute or chronic complications. Diverticulitis can be uncomplicated or complicated. The uncomplicated DD is characterised by colonic wall thickening with fat stranding at computerised tomography (CT); on the contrary complicated DD presents complicating features of abscess, peritonitis, obstruction, fistulas or haemorrhage. Segmental colitis associated with diverticulosis (SCAD) is a unique form of inflammation that occurs in areas marked by diverticulosis. Endoscopic and histological characteristics describe it as a forerunner of inflammatory bowel disease (IBD) (3).

Epidemiology

For many years it has been thought that this type of diverticulosis exclusively affected the westernized world and was due to a lack of fiber intake in the diet

and increased pressure in the colonic wall (4), however, recent data have revealed an increase in the prevalence of colonic diverticulosis throughout the world (5). Necroscopic studies from the first part of the 20th century show a colonic diverticular disease incidence between 2-10% and 5-20% in patients whom underwent a colonoscopy examination (6) being more often encountered in male patients at that time (7). This distribution model is now observed in developing countries. Later studies showed an incidence levelling between genders (8). Studies after the year 2000 showed an increasing incidence up 27% among patients that underwent colonoscopy, being more often encountered in elderly patients (9).

Worldwide incidence of diverticular disease

The anatomic distribution of diverticulosis in the colon also varies by geographic locations. In individuals that reside in western industrialized nations, 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 (10). In Asian population, the anatomic distribution is different and primarily involves the right colon with a rate of approximately 13 to 25% (11). Worldwide diverticular disease has the highest incidence in the United States, Western Europe and Australia (6, 12), reaching 50% in the population aged 60 and above; on the other hand, in sub-Saharan countries the disease is rare and encountered in the 4th decade (13). Nigeria reports an incidence as low as 9.4% among patients that underwent colonoscopy (5), and Calder finds a frequency of diverticular disease of 6.6% in Kenya (14).

The low incidence of diverticular disease in African countries can be due to limited access to healthcare in the general population, and to the low life expectancy in this area (15). On average, the prevalence of diverticular disease among Caucasian Western patients whom underwent barium enema is 15-35%, being equally distributed between genders, but more frequent in the elderly, affecting the left colon in 90-99% of the cases (15, 16). In South-Eastern Asia, the prevalence varies between 8 and 25% (17), reaching a peak in the 5th decade (18, 19) , affecting the right colon in 70-98% of the cases (19) .

Incidence of diverticular disease relative to age

Diverticular disease was first attributed to elderly patients, with a maximal incidence in patients above 70 years old (20). Recent medical literature shows however an increase in diverticulosis incidence in young patients. The most relevant increase was encountered in the group aged 18-44, where the incidence per 1,000 pop. rose from 0.151 to 0.251 in only 7 years. The incidence in patients aged 45- 64 knows

Incidence of diverticular disease around the globe (personal collection using GunnMap)

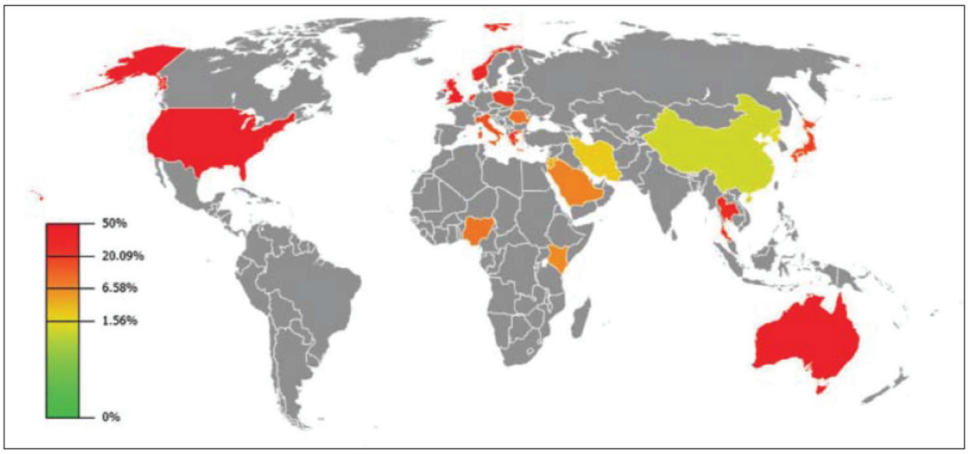

Figure 1. Worldwide incidence of diverticular disease

a lesser increase (from 0.650 to 0.777 over the same period) (21). 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 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 complication and recurrence rate (22).

Gender distribution of diverticular disease

Gender distribution has also changed over the years, initially the diverticular disease being encountered more often in males. However, recent data indicates that males under 50 have a higher incidence of diverticular disease, while after the 4th decade the illness is more frequent in females, as shown by a study from the United Kingdom between 1989 and 2000. Similar results were obtained in Canada, where males under 50 were more prone to diverticular disease (12).

Risk factors

In figure 2 are summarised the current knowledges that will be analysed in this focus on.

AGE: Diverticulosis was first observed in older patients, with a maximal incidence in patients over 70 years old (6), Although advancing age is obviously associated with diverticulosis, this association is not strong *per se*, because the prolonged time course during which the colonic wall is exposed and susceptible to other pathogenetic factors plays an important role (23).

GENETIC FACTORS: Heritability factors also seem to play a role in the development of DD. Some well-defined genetic diseases are associated with a higher incidence of DD. Patients with Ehlers–Danlos syndrome (24), Williams–Beuren (25), Coffin–Lowry (26) and renal polycystic disease (27) are prone to develop diverticula with colonic or other localization. The association with collagen disease can offer regarding the mechanisms that lead to diverticula formation. All these syndromes have in common extracellular matrix defects, suggesting that elastin and collagen accumulation in the smooth muscle may be a prerequisite to diverticula formation (3).

COLONIC MOTILITY: Neural degeneration with age may also contribute to diverticulosis occurrence, with several studies suggesting reduction in neurons in the myenteric plexus (28) and decreased myenteric glial cells and interstitial cells of Cajal (29). Denervation hypersensitivity has also been reported (30), and these abnormalities of enteric nerves might

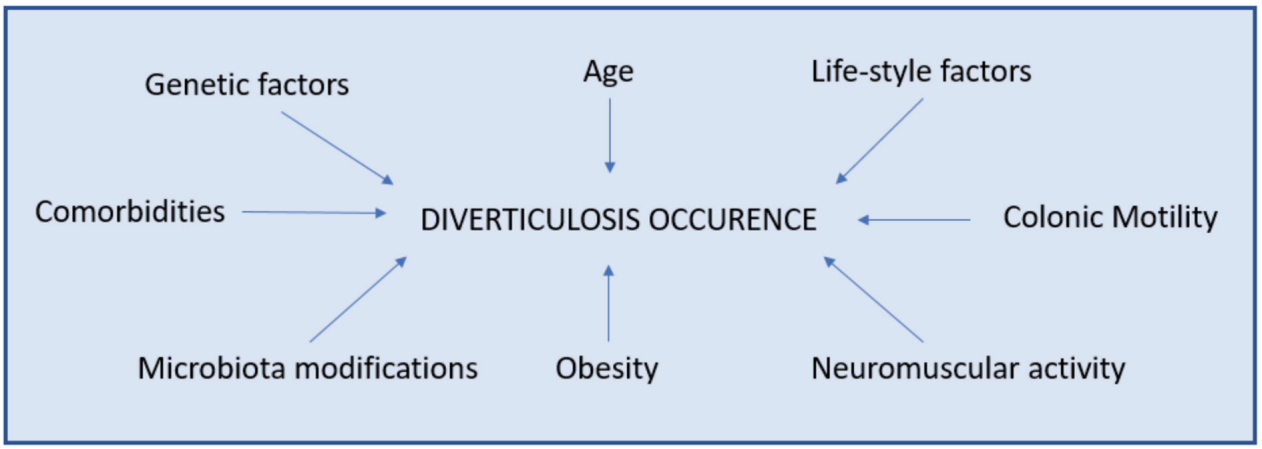

Figure 2. Current knowledges on possible risk factors for diverticulosis occurrence

lead to uncoordinated contractions and high pressure, producing diverticulosis.

NEUROMUSCULAR ACTIVITY: Serotonin is an important neuroendocrine transmitter participating in the control of colonic motor activity through neural and biochemical mechanisms in the enteric nervous system (31). Thus, a possible pathophysiological factor for diverticulosis occurrence has been hypothesized. However, a significant decrease in signalling including content, release, and 5-Hydroxytriptamine (5HT) transporter (SERT) transcript levels was present in the mucosa of patients with a history of diverticulitis compared with controls, but not in those with asymptomatic diverticulosis (32).

FIBRE INTAKE: The old study from Painter and Burkitt found a significantly different diverticulosis prevalence in a western population than in an African population, in which fiber intake is significantly different (6). Two recent colonoscopy-based studies raised the question of the role of fiber intake. Song and colleagues did not find differences in dietary fiber scores between patients with and without diverticulosis assessed by the Mini Dietary Assessment index (33). Moreover, two recent studies conducted in the USA and Japan surprisingly found that dietary fiber intake was positively associated with the presence of diverticulosis (34, 35).

RED MEAT INTAKE: The decrease in fiber intake typically seen with industrialization is paralleled by other dietary changes, including an increase in red meat intake. However, epidemiological studies have provided conflicting results (23). Aldoori and colleagues found significant association between red meat intake and increased risk of DD, even with no dose–response relationship (36). Peery and colleagues did not find any relationship between red meat intake and diverticulosis found at colonoscopy (37).

ALCOHOL INTAKE: There have been conflicting reports on the association of alcohol use and diverticular disease. One of the last meta-analysis found in literature shows that there is no clear association between alcohol consumption and diverticulosis neither diverticular bleeding (38).

SMOKING: The relation between smoking and diverticular disease is debate in literature. Aldoori found smoking was not appreciably associated with risk of symptomatic DD compared with non-smokers (RR=1.25; 95% CI 0.75-2.09) after adjustment for age, physical activity, and energy-adjusted intake of dietary fiber and total fat (39). The recent meta-analysis conducted by Aune on the other hand, provides evidence that tobacco smoking is associated with an increased incidence of diverticular disease and related complications (40).

OBESITY AND PHISICAL ACTIVITY: A relationship between body mass index (BMI) and DD was demonstrated; men with a BMI between 20 and 22.5 kg/m2 had the lowest risk. After adjustment for covariates, the risk increased linearly in men who had a BMI of 22.5-25 (multiple adjusted HR 2.3; 95% CI 0.9-6); 25–27.5 (HR 3; 95% CI 1.2-7.6); 27.5-30 (HR 3.2; 95% CI 1.2-8.6); and 30 or greater (HR 4.4; 95% CI 1.6-12.3) kg/m2 (p for linear trend=0.004) (41). Significantly, neither Strate (42) nor Song (33) found a significant relationship between BMI and diverticulosis detected at colonoscopy.

Physical activity also seems to show the same behaviour, with a significant relationship with reduction of DD complications but with less evidence of diverticulosis occurrence (37, 39, 43, 44).

MICROBIOTA: The detection of small intestinal bacterial overgrowth in patients with diverticulitis supported the hypothesis that bacterial imbalance could play a role in disease occurrence (45). Unfortunately, more recent studies seem inconclusive. Daniels and colleagues recently compared the fecal microbiota of patients with diverticulitis with control subjects from a general gastroenterological practice using a polymerase chain reaction based profiling technique on DNA isolates from fecal samples. They found that Firmicutes/Bacteroidetes ratios and Proteobacteria load were comparable among patients and controls ($p = 0.20$), while a higher diversity in diverticulitis for Proteobacteria ($p < 0.00002$) and all phyla combined ($p = 0.002$) was found (46). Tursi and colleagues recently found no differences in the numbers of rRNA gene copies either for total bacteria or in the different types

analysed in the stool samples comparing patients with Symptomatic Uncomplicated Diverticular Disease (SUDD), patients with acute diverticulitis and healthy controls (47).

MEDICATIONS: Multiple medications have been reported to be associated with diverticular disease. Regular use of nonsteroidal anti-inflammatory drugs and aspirin has been associated with increased risk of diverticular bleeding (48); an increased risk of diverticular disease is also suggested in patients taking steroids and opiates as shown in other studies (49). There is evidence to suggest that statins may have a protective effect against diverticular perforation in patients with diverticulosis (50).

COMORBIDITIES: In literature we can also find the association between diverticulosis and other disease like hypertension and diabetes. Sakuta found that the prevalence rates of type 2 diabetes and hypertension are higher among the middle-aged male subjects with asymptomatic colonic diverticulum (51); moreover Yang provided evidence that the correlation between hypertension and diverticular disease is higher in female patients (52).

Conclusions

Diverticular Disease is a worldwide condition that affect elderly people with an increasing incidence in younger patients as well as in developing countries that have started adopting western diets. Despite its prevalence, its pathophysiology still remains poorly understood and a complexity of factors may play a role in its pathogenesis. There is a significant need for more studies to improve our understanding about risk factors and complications.

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