Pathogenesis of Diverticulosis and Diverticular Disease

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ABSTRACT

In this session different problems regarding the pathogenesis of diverticular disease were considered, including “Genetics”, “Neuromuscular function abnormalities”, “Patterns of mucosa inflammation”, and “Impact of lifestyle”. The patients affected by diverticular disease have clear genetic pattern, that might predispose to the occurrence of the disease as well as to its complications. Neuromuscular abnormalities may be recognized already at the stage of diverticulosis, and inflammation may explain symptoms occurrence in symptomatic uncomplicated diverticulitis (SUD) or symptoms persistence after an episode of acute diverticulitis. Finally, lifestyle might also have an impact on symptoms’ occurrence. Specifically smoking, but also obesity seem to play an important role, while the role of low-fiber diet and constipation is now under debate.

Key words: diverticular disease – acute diverticulitis – colonoscopy – genetics – fiber - low-grade inflammation – neuromuscular alteration – symptomatic uncomplicated diverticular disease.

Abbreviations: DD: diverticular disease; SCAD: segmental colitis associated with diverticulosis; SUDD: symptomatic uncomplicated diverticular disease.

GENETICS

Diverticular disease (DD) of the colon is a common disease with an increasing impact for the National Health Systems [1]. It is a complex disorder resulting from an interaction of multiple factors; however, the exact pathogenesis of this disease is not known. Gathered evidence suggests that genetic factors contribute to the development of DD [2]. Convincing data that support the role of genetic factors in DD come from monogenic disorders of connective tissue syndromes, including Williams-Beuren syndrome, Coffin-Lowry syndrome and Autosomal Dominant Polycystic Kidney Disease where colon diverticula occur at a very early age [2]. A couple of epidemiological twin studies have also recently pointed to the significant role of inherited factors in the development of DD [3, 4]. Several small case-control studies have initially attempted to identify certain single nucleotide polymorphisms (SNPs), but were underpowered to provide significant findings [5, 6]. A larger case control study including 422 patients with diverticulosis and 285 controls found that variant rs3134646 in COL3A1 gene is associated with the risk of developing colonic diverticulosis in men [7]. However, the most important data on genetic predisposition of DD come from three very recent genome-wide association studies (GWAS) [7-9]. The first GWAS on Iceland population showed that variants in ARHGAP15 and COLQ genes were linked with uncomplicated DD and variants in FAM155A were associated with diverticulitis [8]. Additionally, 37 susceptibility loci with genome-wide significance were identified in a recent study from Maguire et al. [9] with replication of 8 loci. The largest GWAS study to date employed UK Biobank and imputed nucleotide polymorphisms (SNPs), but were underpowered to provide significant findings [5, 6]. A larger case control study including 422 patients with diverticulosis and 285 controls found that variant rs3134646 in COL3A1 gene is associated with the risk of developing colonic diverticulosis in men [7]. However, the most important data on genetic predisposition of DD come from three very recent genome-wide association studies (GWAS) [7-9]. The first GWAS on Iceland population showed that variants in ARHGAP15 and COLQ genes were linked with uncomplicated DD and variants in FAM155A were associated with diverticulitis [8]. Additionally, 37 susceptibility loci with genome-wide significance were identified in a recent study from Maguire et al. [9] with replication of 8 loci. The largest GWAS study to date employed UK Biobank and imputed genotypes using 31 964 cases and 419 135 controls [10]. These associations were then replicated in a European sample of 3893 cases and 2829 diverticula-free controls and evaluated for risk contribution to diverticulitis and uncomplicated diverticulosis and identified 48 genetic risk loci [10]. The genetic data from all three GWAS studies clearly show that DD primarily is a disorder of intestinal neuromuscular function and of impaired connective fibre support, while an additional diverticularitis risk might be conferred by epithelial dysfunction related genes [8-10]. To date, there are no studies evaluating how identified
The presence of inflammation, diverticulitis - macroscopic inflammation of diverticula with related acute or chronic complications is seen in 4% of those with diverticulosis (with an 11-year follow up) and 11% in younger patients (40-49 yrs) [20]. In the patients with acute inflammatory complications of DD, inflammation in the mucosa is evident and acute in nature. When complications ensue and diverticula break, an acute abdomen leads to surgical intervention and consequent surgical pathology shows full thickness and peritoneal inflammation. Segmental colitis associated with diverticula (SCAD), a unique form of mucosal or full thickness inflammation that looks similar with IBD, is observed in 11% of those with diverticulosis and 2% of patients investigated by colonoscopy [21-23]. This is a specific mucosal inflammatory process, confined to the sigmoid and descending colon. In SUDD, the site of inflammation is likely deep in the muscularis and may interact with nerves, as patients exhibit visceral hypersensitivity, and this may be mediated by ongoing low grade inflammation and upregulation of tachykinins [18].

In conclusion, neuromuscular dysfunction plays a paramount role in DD, but more investigations are needed to establish the true role of this dysfunction.


diverticulosis [30, 31]. Physical activity, especially vigorous activity, also decreases the risk of diverticulitis [32]. On the other hand, red meat consumption is positively associated with risk of incident diverticulitis [28, 29], although the association between fiber and asymptomatic diverticulosis is uncertain [30, 31]. In a large UK cohort, individuals who consumed more than 25 grams of fiber had a 40% decreased risk of hospitalization for diverticulitis [28], but two cross-sectional colonoscopy studies found no association between fiber intake and asymptomatic diverticulosis [30, 31]. Physical activity, especially vigorous activity, also decreases the risk of diverticulitis [32]. On the other hand, red meat consumption is positively associated with risk of diverticulitis (relative risk 1.2 for each serving of red meat) [33]. When considering diet as a whole, a Western dietary pattern (high in red meat and refined grains), increases risk of diverticulitis, whereas a prudent pattern (high in fruits, vegetables and whole grains) decreases risk [34]. Obesity, and central obesity in particular, is associated with risk of diverticulitis. In a prospective study, men with a body mass index (BMI) > 30 kg/m2 had a relative risk of 1.8 [35]. Weight
gain also contributes to the risk of diverticulitis [36]. Smoking is another risk factor especially for complicated diverticulitis (37,38). The importance of diet and lifestyle is demonstrated in a study that found that men who adhered to five healthy lifestyle factors (BMI 18-25 kg/m2, fiber intake > 23 g/day, red meat < 4 servings/week, two hours of exercise/week and no smoking had a 75% decreased diverticulitis risk compared to men who did not adhere to any healthy lifestyle factors [39].

**REFERENCES**


J Gastrointestin Liver Dis, 2019 Vol. 28 Suppl 4: 7-10