Medicine®

OBSERVATIONAL STUDY

OPEN

Association Between Colonic Diverticulosis and Erectile Dysfunction

A Nationwide Population-Based Study

Chia-Chang Chen, MD, MSc, Jiann-Sheng Su, MD, Hong-Zen Yeh, MD, Chi-Sen Chang, MD, PhD, Yen-Chun Peng, MD, Chih-Wei Tseng, MD, Yu-Tso Chen, MD, Cheng-Li Lin, MSc, and Chia-Hung Kao, MD

Abstract: We investigated whether colonic diverticulosis (CD) is associated with an increased risk of the subsequent development of erectile dysfunction (ED).

We identified 2879 patients, diagnosed with CD between 1998 and 2011 from the Taiwan National Health Insurance Research Database as the study cohort. Patients in a comparison cohort were frequency-matched with those in the CD cohort at a ratio of 1:4, frequency matched according to age (in 5-year bands) and year of CD diagnosis. The patients were followed-up until ED development, withdrawal from the National Health Insurance system, or the end of 2011. For both cohorts, the overall and age-specific incidence density rates of ED (per 1000 person-years) were calculated. The effects of age, CD, and other comorbidities on the risk of ED development were examined using Cox proportional hazards regression models.

The average follow-up durations were 4.76 years and 4.97 years for the CD patients and comparison cohorts, respectively. The overall incidence of ED was 1.70-fold higher in the CD cohort than in the comparison cohort (2.92 and 1.71 per 1000 person-years, respectively). Colonic diverticulosis was an independent risk factor for subsequent ED development (adjusted HR [aHR] = 1.56, 95% confidence interval = 1.07–2.28) in a multivariate Cox proportional hazards regression model.

In this large retrospective cohort study, CD was associated with future ED development. Additional studies are required for validating our results.

(*Medicine* 94(47):e2042)

Abbreviations: CAD = coronary artery disease, CD = colonic diverticulosis, CIs = confidence intervals, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, ED = erectile dysfunction, HRs = hazard ratios, IBS = irritable bowel syndrome, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, IRB = Institutional Review Board, NHI = Taiwan's National Health Insurance, NHIRD = National Health Insurance Research Database, NHRI = National Health Research Institute, SUDD = symptomatic uncomplicated diverticular disease.

INTRODUCTION

Colonic diverticulosis (CD) is the herniation of the colonic mucosa through the circular muscle layer at various points. The underlying pathological mechanisms that cause the formation of colonic diverticula remain unknown.[1] The prevalence of CD is estimated 13.5% in Taiwan and even higher in older people (up to 71.4% for age > 80 years in USA).[2,3] The common complications of CD include abdominal pain, diverticulitis, peritonitis, obstruction, fistulization, or abscess formation.[4,5] In addition to these recurrent acute complications and chronic abdominal pain, model theories suggested that CD can cause some chronic disease and effect qualities of life.[6] Chronic inflammation and microbiome shifts are potential etiologic factors for CD.[7–11] Chronic inflammation plays a role in the pathogenesis of cardiovascular disease, venous thromboembolism, and arterial atherosclerosis.[12] Therefore, CD may increase relevant diseases associated with this condition. For example, CD was recently found to increase the risk of arterial and venous thromboembolic events.[13]

Erectile dysfunction (ED) is a consistent or recurrent inability to obtain or maintain penile erection sufficient for sexual activity. The prevalence of ED increases with age and

Editor: Somchai Amornyotin.
Received: July 28, 2015; revised: September 21, 2015; accepted: September 24, 2015.
From the Division of Gastroenterology and Hepatology, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan (C-CC, H-ZY, C-SC, Y-CP); Division of Gastroenterology and Hepatology, Kuang Tien General Hospital, Taichung, Taiwan (J-SS); Division of Allergy, Immunology and Rheumatology, Taichung Veterans General Hospital, Taichung, Taiwan (C-WT); Division of Gastroenterology and Hepatology, Department of Internal Medicine, Feng Yuan Hospital Ministry of Health and Welfare, Taichung, Taiwan (Y-TC); Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan (C-LL); College of Medicine, China Medical University, Taichung, Taiwan (C-LL); Graduate Institute of Clinical Medical Science and School of Medicine, College of Medicine, China Medical University, Taichung, Taiwan (C-HK); and Department of Nuclear Medicine and PET Center, China Medical University Hospital, Taichung, Taiwan (C-HK).
Correspondence: Chia-Hung Kao, Graduate Institute of Clinical Medical Science, College of Medicine, China Medical University, No. 2, Yuh-Der Road, Taichung, Taiwan (e-mail: d10040@mail.cmuh.org.tw).
Author contributions: All authors have contributed substantially to, and are in agreement with the content of, the manuscript—conception/design: Chia-Chang Chen, Chia-Hung Kao; provision of study materials: Chia-Hung Kao; collection and/or assembly of data: all authors; data analysis and interpretation: all authors; manuscript preparation: all authors; final approval of manuscript: all authors.
Funding: this study is supported, in part, by Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW104-TDU-B-212-113002); China Medical University Hospital, Academia Sinica Taiwan Biobank, Stroke Biosignature Project (BM104010092); NRPB Stroke Clinical Trial Consortium (MOST 103-2325-B-039 -006); Tseng-Lien Lin Foundation, Taichung, Taiwan; Taiwan Brain Disease Foundation, Taipei, Taiwan; Katsuzo and Kiyo Aoshima Memorial Funds, Japan; and CMU under the Aim for Top University Plan of the Ministry of Education, Taiwan. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. No additional external funding received for this study.
The authors have no conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000002042

can reach 20% to 40% for men in their 60 s.[14] Evidence has shown that ED is associated with cardiovascular disease and coronary artery disease (CAD).[15,16] Erectile dysfunction was considered a predictor of silent CAD in diabetic populations.[17] Studies also found that ED became evident before angina symptoms[18] and preceded CAD by an average of 2 to 3 years.[19] Subclinical endothelial dysfunction and low-grade inflammation may be the underlying pathogenesis of ED.[20]

Colonic diverticulosis was closely linked to chronic inflammation and thromboembolism which were important etiological factors of ED. It is possible that CD can increase ED. So we conducted a large population-based cohort study to see if CD was associated with ED.

METHOD

Data Source

The National Health Insurance Research Database (NHIRD) is derived from the mandatory single-payer National Health Insurance (NHI) program initiated by the Taiwan government in 1995. By 2014, >24 million people, representing ~99% of the population of Taiwan, were covered by the NHI program.[21] In this study, we analyzed data from the Longitudinal Health Insurance Database 2000, a subset of the NHIRD that contains the data of 1,000,000 randomly sampled patients, who were traced retrospectively to 1996 and followed-up to 2011. The National Health Research Institute (NHRI) has confirmed these random samples as representative of the general population of Taiwan. The NHRI safeguards the privacy of patients and provides data to researchers after ethical approval has been obtained. This retrospective study was approved to fulfill the condition for exemption by the Institutional Review Board (IRB) of China Medical University (CMUH-104-REC2-115). The IRB also specifically waived the consent requirement.

Sampled Participants

Male patients, aged 20 years and older and newly diagnosed with CD (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 562.10, 562.11, 562.12, 562.13) from 1998 to 2011, were identified as the CD cohort. The date of CD diagnosis was considered the index date. Patients with a history of ED (ICD-9-CM codes 302.72, 607.84) diagnosed before the index date, with missing information, and aged <20 years were excluded. The comparison cohort included patients without a history of CD or ED, frequency-matched with the CD cohort patients at a ratio of 1:4 for age (in 5-year bands) and year of CD diagnosis by using the same exclusion criteria. The index date for comparison subjects was randomly appointed a month and day with the same index year of the matched CD cases.

Outcome and Comorbidities

The main outcome was outpatient visits or hospitalization with a new diagnosis of ED during the follow-up. The duration of follow-up was estimated from the index date until ED occurred, withdrawal from the insurance system, or the end of 2011. Baseline comorbidities included CAD (ICD-9-CM codes 410–414), chronic obstructive pulmonary disease (COPD) (ICD-9-CM codes 491, 492, 496), chronic kidney disease (CKD) (ICD-9-CM codes 580–589), hypertension (ICD-9-CM codes 401–405), diabetes (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), depression (ICD-9-CM codes 296.2–296.3, 300.4, 311), stroke (ICD-9-CM codes 430–438), asthma (ICD-9-CM code 493), and alcohol-related illness (ICD-9-CM codes 291, 303, 305, 571.0, 571.1, 571.2, 571.3, 790.3, A215, and V11.3).

Statistical Analyses

The distribution of categorical demographic characteristics and comorbidities were compared between CD and comparison cohorts. Differences were examined using the chi-square test for categorical variables. The mean ages and follow-up periods were measured and examined using a Student *t* test. The overall and age-specific incidence density rates of ED (per 1000 person-years) were calculated. Univariate and multivariate Cox proportional hazards regression models were used for examining the effects of CD on the risk of ED, and shown as hazard ratios (HRs) with 95% confidence intervals (CIs). The multivariate models were simultaneously adjusted for age and the comorbidities of CAD, COPD, CKD, hypertension, diabetes, hyperlipidemia, depression, stroke, asthma, and alcohol-related illness. A Kaplan–Meier analysis plot was used for showing the cumulative incidence of ED, and log-rank test was used for examining the differences between the 2 cohorts. All data analyses were conducted using SAS statistical software (version 9.3 for Windows; SAS Institute Inc., Cary, NC). Two-tailed $P < .05$ was considered significant.

RESULTS

Eligible study participants comprised 2879 patients in the CD cohort and 11,504 persons in the comparison cohort, with a similar age distribution (Table 1). The mean age in the CD and comparison cohorts were 55.2 (SD = 17.7) years and 54.6 (SD = 17.8) years, respectively. At baseline, the comorbidities of CAD, COPD, CKD, hypertension, diabetes, hyperlipidemia, depression, stroke, asthma, and alcohol-related illness were

TABLE 1. Demographic Characteristics and Comorbidities in Cohorts With and Without Colonic Diverticulosis

	Diverticular		
	No	Yes	
Variable	**N = 11504**	**N = 2879**	***P* Value**
Age, year	n (%)	n (%)	0.99
≤ 39	2701 (23.5)	675 (23.5)	
40–59	4106 (35.7)	1027 (35.7)	
60+	4697 (40.8)	1177 (40.9)	
Mean ± SD*	54.6 (17.8)	55.2 (17.7)	0.15
Comorbidity			
CAD	1898 (16.5)	800 (27.8)	<0.001
COPD	1637 (14.2)	645 (22.4)	<0.001
CKD	825 (7.17)	389 (13.5)	<0.001
Hypertension	3861 (33.6)	1279 (44.4)	<0.001
Diabetes	1095 (9.52)	334 (11.6)	<0.001
Hyperlipidemia	2132 (18.5)	800 (27.8)	<0.001
Depression	417 (3.62)	208 (7.22)	<0.001
Stroke	608 (5.29)	231 (8.02)	<0.001
Asthma	1456 (12.7)	539 (18.7)	<0.001
Alcohol-related illness	596 (5.18)	325 (11.3)	<0.001

CAD = coronary artery disease, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, SD = standard deviation.
* Chi-square test; *t* test.

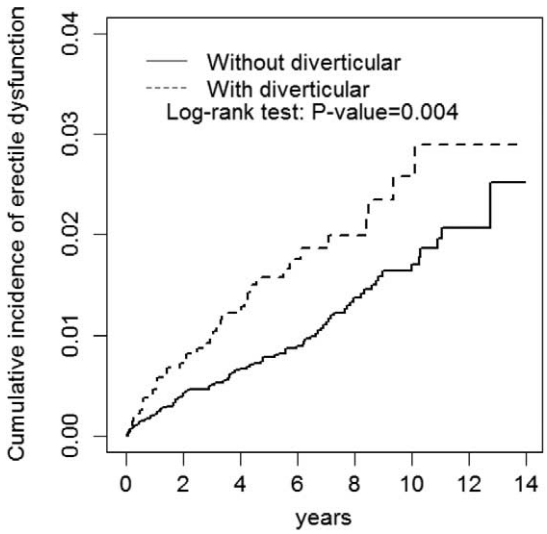

FIGURE 1. Cumulative incidence comparison of erectile dysfunction in patients with (dashed line) or without (solid line) colonic diverticulosis.

more prevalent in the CD cohort than in the comparison cohort. The average follow-up duration was 4.76 years for patients with CD and 4.97 years for the comparison cohort. Kaplan–Meier analysis showed that the cumulative incidence of ED after 14 years of follow-up was higher in the CD cohort than in the comparison cohort (log-rank test, $P = 0.004$, Figure 1). The overall incidence of ED was 1.70-fold higher in the CD cohort than in the comparison cohort (2.92 and 1.71 per 1000 person-years, respectively, Table 2). After we adjusted for age and the comorbidities of CAD, COPD, CKD, hypertension, diabetes, hyperlipidemia, depression, stroke, asthma, and alcohol-related illness, patients with CD were associated with an increased risk of ED compared with those without CD (aHR = 1.56, 95% CI = 1.07–2.28). The age-specific incidence and relative risk of ED were highest for men aged ≥60 years in the CD cohort (3.46 per 1000 person-years, aHR = 1.97, 95% CI = 1.09–3.56). We analyzed the association between CD and the risk of ED stratified by comorbidity and found an ∼1.50-fold ED risk was observed in patients without comorbidities (adjusted HR = 1.50, 95% CI: 1.22–3.13).

The results of multivariate Cox proportional hazard regression models for the risk of related variables contributing to ED are shown in Table 3. The risk of developing ED increased 3.16-fold (95% CI = 1.84–5.45) with the comorbidity of depression and 1.71-fold (95% CI = 1.06–2.76) with the comorbidity of asthma. Furthermore, CD patients with depression were at a higher risk of ED than comparison patients without depression (aHR = 4.71, 95% CI = 2.13–10.4, Table 4). Relative to the patients without CD and asthma, the CD patients with asthma were at a higher risk of ED (aHR = 2.22, 95% CI = 1.02–4.84).

DISCUSSION

To best of our knowledge, this is the first study to investigate the association between CD and ED by using a nationwide population database. Patients with CD had an increased risk of developing ED after adjusting major comorbidities. The patients with CD had 1.56-fold higher incidence of ED than non-CD patients. We also found that depression and asthma were associated with ED. The CD patients with depression had the highest incidence of ED.

Alcohol consumption and smoking habit are important risk factors for ED.[22] Similarly, alcohol consumption and smoking are also risk factors for CD.[23,24] Could the increase in ED on the CD group observed be due to an increased alcohol consumption and smoking in the CD group? To minimize the influence from smoking and alcohol, we used an alternative way and adjusted for smoking-related diseases (including COPD, CAD, stroke, asthma) and alcohol-related illness in our analysis. After we

TABLE 2. Incidence of Erectile Dysfunction According to Age and Comorbidities, and Cox Model-Measured Hazard Ratios for Patients With Colonic Diverticulosis Compared With Those Without Colonic Diverticulosis

	Diverticular							
	No			Yes				
Variables	Event	PY	Rate†	Event	PY	Rate†	Crude HR‡ (95% CI)	Adjusted HR§ (95% CI)
All	98	57174	1.71	40	13713	2.92	1.70 (1.18, 2.46)**	1.56 (1.07, 2.28)**
Stratify age								
≤ 59	63	35171	1.79	22	8517	2.58	1.45 (0.89, 2.35)	1.20 (1.02, 1.41)*
60+	35	22003	1.59	18	5196	3.46	2.16 (1.22, 3.80)**	1.97 (1.09, 3.56)**
Comorbidity‖								
No	41	30909	1.33	10	5223	1.91	1.44 (1.17, 1.78)**	1.50 (1.22, 3.13)**
Yes	57	26265	2.17	30	8491	3.53	1.63 (1.40, 1.90)**	1.61 (1.04, 2.51)**

CI = confidence interval, HR = hazard ratio, PY = person-years.

†Rate, incidence rate, per 1000 person-years;

‡Crude HR, relative hazard ratio;

§Adjusted HR: multivariable analysis including age, and comorbidities of CAD, COPD, CKD, hypertension, diabetes, hyperlipidemia, depression, stroke, asthma, and alcohol-related illness.

‖Comorbidity§: patients with any one of the comorbidities (including CAD, COPD, CKD, hypertension, diabetes, hyperlipidemia, depression, stroke, asthma, and alcohol-related illness) were classified as the comorbidity group.

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

TABLE 3. Hazard Ratios of Erectile Dysfunction in Association With Age and Comorbidities in Univariable and Multivariable Cox Regression Models

	Crude†	Adjusted‡
Variable	**HR (95% CI)**	**HR (95% CI)**
Diverticular	1.70 (1.18, 2.46)**	1.56 (1.07, 2.28)**
Age, years	1.01 (1.00, 1.02)*	1.00 (0.99, 1.02)
Baseline comorbidities (yes vs no)		
CAD	1.68 (1.14, 2.47)**	1.13 (0.70, 1.80)
COPD	1.28 (0.82, 2.01)	0.73 (0.43, 1.25)
CKD	1.47 (0.84, 2.55)	1.06 (0.59,1 .90)
Hypertension	1.69 (1.21, 2.36)**	1.34 (0.86, 2.09)
Diabetes	1.66 (1.00, 2.77)	1.32 (0.76, 2.29)
Hyperlipidemia	1.38 (0.93, 2.05)	0.99 (0.63, 1.53)
Depression	3.55 (2.11, 5.99)***	3.16 (1.84, 5.45)***
Stroke	2.08 (0.66, 6.53)	3.27 (0.99, 10.4)
Asthma	1.92 (1.25, 2.95)**	1.71 (1.06, 2.76)***
Alcohol-related illness	0.47 (0.15, 1.48)	0.36 (0.11, 1.15)

CAD = coronary artery disease, CI = confidence interval, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, SD = standard deviation, HR = hazard ratio.

†Crude HR, relative hazard ratio

‡Adjusted HR: multivariable analysis including age and comorbidities of CAD, hypertension, and depression

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

adjusted for age and comorbidities, the CD patients still exhibited a significantly increase risk of ED than did the comparison cohort. We speculated that the increase of ED incidence in our CD patients cannot be fully explained by sharing similar risk factors.

The exact pathophysiology of CD leading to ED is not clear. Chronic inflammation, an important mechanism of CD, may be possible reason for increasing subsequent ED. It is widely accepted that chronic intestinal inflammation may cause a low-grade inflammation status in CD patients.[6–8] Lymphocytic inflammation of colon was noted in CD patients without overt colitis.[25] Also, colon mucosa around the diverticula from patients who underwent surgery for symptomatic uncomplicated diverticular disease (SUDD) often demonstrated chronic inflammation.[26] Some indirect evidence supports a potential association between intestinal microbiota and CD, therefore leading to chronic inflammation. For example, Rifaximin, a nonsystemic antibiotic, may reduce the attacks of recurrent diverticulitis and treat gastrointestinal symptoms in patients with SUDD.[9,10] A low-fiber diet may change gut microbiota and is a possible risk factor for CD.[11] Bacteria overgrowth was also observed in patients with uncomplicated acute diverticulitis.[27] Chronic inflammation was known as a pathologic factor of cardiovascular disease, venous thromboembolism, and arterial atherosclerosis.[12] This was demonstrated by the fact that both inflammatory bowel disease and CD were associated with vascular disease and thromboembolic events.[13,28,29] ED was closely linked to chronic inflammation and vascular disease.[15,20] Increased inflammatory and endothelial-prothrombotic activation were significantly increased in patients with ED.[30] Atherosclerosis of penis arteries was proposed as the vascular etiology of ED.[31] These sharing pathophysiological factors between ED and CD may support our study findings. In our study, we also found that asthma was an independent risk of ED (aHR: 1.71, 95% CI: 1.06–2.76). We think this finding can also be explained by the fact that asthma is also associated with systemic inflammation.[32–34] Asthma was also found to increase ED risk in another population-based study.[35] The author also proposed that systemic inflammation may subsequently contribute to endothelial dysfunction, which is central to the pathogenesis of ED.

TABLE 4. Cox Proportional Hazard Regression Analysis for the Risk of Erectile Dysfunction-Associated Colonic Diverticulosis Combined With the Effect of Comorbidities

Variables		Event	Rate†	Adjusted HR‡ (95% CI)
Colonic diverticulosis	Depression			
No	No	90	1.62	1 (Reference)
No	Yes	9	5.54	3.29 (1.64, 6.63)***
Yes	No	33	2.57	1.58 (1.06, 2.37)*
Yes	Yes	7	7.94	4.71 (2.13, 10.4)***
Colonic diverticulosis	Asthma			
No	No	80	1.55	1 (Reference)
No	Yes	18	3.27	1.94 (1.12, 3.37)*
Yes	No	32	2.75	1.69 (1.11, 2.56)*
Yes	Yes	8	3.82	2.22 (1.02, 4.84)*

CI = confidence interval, HR = hazard ratio, PY, person-years.

+Rate, incidence rate per 10,000 person-years

ÂAdjusted HR, hazard ratio adjusted for age, and other comorbidities

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Our study result suggested that both depression and CD are independent risk factors for ED. Depressive symptoms are established as a definite risk factor for ED.[36] Could the coexisted depression in CD patients is the true causal factor to subsequent ED? Indeed, CD patients reported lower health-related quality of life and higher emotional stress than controls. And CD patients also had higher incidence of anxiety and stress than no-CD patients.[37–39] However, depression significantly affects CD patients not only in psychological dimension. For example, increased depression and anxiety are known to associate with recurrent pain in CD patients, independent of previous colonic inflammation (like history of acute diverticulitis).[39] Thus, CD patients may have more gastrointestinal symptoms if they had depressed mood. On the other hand, the severity of gastrointestinal symptoms in other function gastrointestinal diseases like irritable bowel syndrome (IBS) and functional dyspepsia has been demonstrated to be positively associated with sexual dysfunction, independent of psychological symptom severity.[40] Irritable bowel syndrome and CD are closely related.[41] Diverticulitis appears to predispose patients to long-term gastrointestinal and emotional symptoms after resolution of inflammation, which is called postdiverticulitis IBS.[42] But it is also possible that ongoing gastrointestinal symptoms after a diverticulitis attack result from recurrent low-grade diverticulitis. Part of CD patients may suffer from chronic pain and depression that persist out of their acute attack. From aforementioned study findings, depression and bowel symptoms are both independent risk factors for ED. This was also compatible with our study finding, which suggested that depression and CD had a synergic effect to

increase ED risk (aHR = 4.71, 95% CI = 2.13–10.4, Table 4). It may be warranted that we may need to care both depression and bowel symptoms of CD patients, which may cause subsequent ED.

Study Limitations

This study had several limitations. First, the NHIRD does not contain detailed personal information, such as smoking habit, alcohol consumption, BMI, physical activity level, and body habitus. Consequently, we could not adjust for these factors, which may have influenced our results. But we had tried to eliminate the effect of smoking and alcohol by adjusting related disorders. Second, ICD-9-CM codes, instead of detailed medical history, image diagnosis, and patient self-reported questionnaire data, were used for assigning patients with CD and ED. Third, the incidence of CD locations is different from east countries to west countries. Colonic diverticulosis was dominantly on the right side in patients in Japan, in contrast to those in Europe and the United States.[43] We did not have information about the location of diverticulum from the NHIRD database. So we are not sure the same result can reproduced in west countries. Finally, this was a retrospective cohort study, consequently making bias and confounders inevitable. But the large sample size of our study affords considerable statistical power for detecting real, even subtle, differences between the 2 cohorts. Additional well-designed population-based studies may confirm our findings.

CONCLUSION

In this large retrospective cohort study, we demonstrated that CD patients may have a higher risk of developing ED than non-CD patients did. The CD patients with depression had even higher risk of developing ED. Our findings support the evolving paradigm of diverticular disease as a chronic illness, which impacts on qualities of life and sexual health of our patients. It is very important that physicians should not to see CD as a merely recurrent acute illness. They should start to be awareness of potential concurrent physical and psychological stress of these patients and take action to manage them. Additional studies are also required for confirming the association between CD and ED. If the association were proved, it is also important to know whether treatment for diverticulosis can slow the development or progression of ED.

REFERENCES

1. Simpson J, Scholefield JH, Spiller RC. Pathogenesis of colonic diverticula. *Br J Surg.* 2002;89:546–554.
2. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States Part II: lower gastrointestinal diseases. *Gastroenterology.* 2009;136:741–754.
3. Wang F-W, Chuang H-Y, Tu M-S, et al. Prevalence and risk factors of asymptomatic colorectal diverticulosis in Taiwan. *BMC Gastroenterol.* 2015;15:40.
4. Parks TG. Natural history of diverticular disease of the colon. *Clin Gastroenterol.* 1975;4:53–69.
5. Stollman NH, Raskin JB. Diagnosis and management of diverticular disease of the colon in adults. Ad Hoc Practice Parameters Committee of the American College of Gastroenterology. *Am J Gastroenterol.* 1999;94:3110–3121.
6. Strate LL, Modi R, Cohen E, et al. Diverticular disease as a chronic illness: evolving epidemiologic and clinical insights. *Am J Gastroenterol.* 2012;107:1486–1493.
7. Colecchia A, Sandri L, Capodicasa S, et al. Diverticular disease of the colon: new perspectives in symptom development and treatment. *World J Gastroenterol.* 2003;9:1385–1389.
8. Floch MH, White J. Diverticulitis: new concepts and nw therapies. *J Clin Gastroenterol.* 2005;39:355–356.
9. Littlewood ER, Ornstein MH, Baird IM, Cox AG. Doubts about diverticular disease. *British Med J.* 1981(Clinical research ed.) (Vol. 283). doi:10.1136/bmj.283.6305.1524.
10. Tursi A, Brandimarte G, Daffinà R. Long-term treatment with mesalazine and rifaximin versus rifaximin alone for patients with recurrent attacks of acute diverticulitis of colon. *Dig Liver Dis.* 2002;34:510–515.
11. Korzenik JR. Case closed? Diverticulitis: epidemiology and fiber. *J Clin Gastroenterol.* 2006;40(Suppl 3):S112–S116.
12. Pai JK, Pischon T, Ma J, et al. Inflammatory markers and the risk of coronary heart disease in men and women. *N Engl J Med.* 2004;351:2599–2610.
13. Strate LL, Erichsen R, Horváth-Puhó E, et al. Diverticular disease is associated with increased risk of subsequent arterial and venous thromboembolic events. *Clin Gastroenterol Hepatol.* 2013;12:1695–1701e1.
14. Lewis RW, Fugl-Meyer KS, Corona G, et al. Definitions/epidemiology/risk factors for sexual dysfunction. *J Sex Med.* 2010;7:1598–1607.
15. Dong J-Y, Zhang Y-H, Qin L-Q. Erectile dysfunction and risk of cardiovascular disease meta-analysis of prospective cohort studies. *J Am Coll Cardiol.* 2011;58:1378–1385.
16. Jackson G, Boon N, Eardley I, et al. Erectile dysfunction and coronary artery disease prediction: evidence-based guidance and consensus. *Int J Clin Pract.* 2010;64:848–857.
17. Gazzaruso C, Giordanetti S, De Amici E, et al. Relationship between erectile dysfunction and silent myocardial ischemia in apparently uncomplicated type 2 diabetic patients. *Circulation.* 2004;110:22–26.
18. Montorsi F, Briganti A, Salonia A, et al. Erectile dysfunction prevalence, time of onset and association with risk factors in 300 consecutive patients with acute chest pain and angiographically documented coronary artery disease. *Eur Urol.* 2003;44:360–365.
19. Montorsi P, Ravagnani PM, Galli S, et al. Association between erectile dysfunction and coronary artery disease. Role of coronary clinical presentation and extent of coronary vessels involvement: the COBRA trial. *Eur Heart J.* 2006;27:2632–2639.
20. Yao F, Huang Y, Zhang Y, et al. Subclinical endothelial dysfunction and low-grade inflammation play roles in the development of erectile dysfunction in young men with low risk of coronary heart disease. *Int J Androl.* 2012;35:653–659.
21. Database NHIR. Taiwan, http://nhird.nhri.org.tw/en/Background.html (cited in 2015).
22. Bacon CG, Mittleman MA, Kawachi I, et al. Sexual function in men older than 50 years of age: results from the health professionals follow-up study. *Ann Intern Med.* 2003;139:161–168+I22.
23. Nagata N, Niikura R, Shimbo T, et al. Alcohol and smoking affect risk of uncomplicated colonic diverticulosis in Japan. *PLoS One.* 2016;8:e81137.
24. Sharara AI, El-Halabi MM, Mansour NM, et al. Alcohol consumption is a risk factor for colonic diverticulosis. *J Clin Gastroenterol.* 2016;47:420–425.
25. Floch MH. A hypothesis: is diverticulitis a type of inflammatory bowel disease? *J Clin Gastroenterol.* 2006;40(Suppl 3):S121–S125.
26. Horgan AF, McConnell EJ, Wolff BG, et al. Atypical diverticular disease: surgical results. *Dis Colon Rectum.* 2001;44:1315–1318.
27. Tursi A, Brandimarte G, Giorgetti GM, et al. Assessment of small intestinal bacterial overgrowth in uncomplicated acute diverticulitis of the colon. *World J Gastroenterol.* 2005;11:2773–2776.

28. Balzola F, Bernstein C, Ho GT, et al. Thromboembolic risk among Danish children and adults with inflammatory bowel diseases: a population-based nationwide study—Commentary. *Inflamm Bowel Dis Monit.* 2011;12:76.
29. Fumery M, Xiaocang C, Dauchet L, et al. Thromboembolic events and cardiovascular mortality in inflammatory bowel diseases: a meta-analysis of observational studies. *J Crohns Colitis.* 2014;8:469–479.
30. Vlachopoulos C, Aznaouridis K, Ioakeimidis N, et al. Unfavourable endothelial and inflammatory state in erectile dysfunction patients with or without coronary artery disease. *Eur Heart J.* 2006;27: 2640–2648.
31. Montorsi P, Ravagnani PM, Galli S, et al. The artery size hypothesis: a macrovascular link between erectile dysfunction and coronary artery disease. *Am J Cardiol.* 2005;96(12 Suppl 2).
32. Takemura M, Matsumoto H, Niimi A, et al. High sensitivity C-reactive protein in asthma. *Eur Respir J.* 2006;27:908–912.
33. Kony S, Zureik M, Driss F, et al. Association of bronchial hyperresponsiveness and lung function with C-reactive protein (CRP): a population based study. *Thorax.* 2004;59:892–896.
34. Jousilahti P, Salomaa V, Hakala K, et al. The association of sensitive systemic inflammation markers with bronchial asthma. *Ann Allergy Asthma Immunol.* 2002;89:381–385.
35. Chou KT, Huang CC, Chen YM, et al. Asthma and risk of erectile dysfunction—A nationwide population-based study. *J Sex Med.* 2011;8:1754–1760.
36. Araujo AB, Durante R, Feldman HA, et al. The relationship between depressive symptoms and male erectile dysfunction: cross-sectional results from the Massachusetts Male Aging Study. *Psychosom Med.* 1998;60:458–465.
37. Bolster LT, Papagrigoriadis S. Diverticular disease has an impact on quality of life—results of a preliminary study. *Colorectal Dis.* 2003;5:320–323.
38. Comparato G, Fanigliulo L, Aragona G, et al. Quality of life in uncomplicated symptomatic diverticular disease: is it another good reason for treatment? *Dig Dis.* 2007;25:252–259.
39. Humes DJ, Simpson J, Neal KR, Scholefield JH, Spiller RC. Psychological and colonic factors in painful diverticulosis. *Br J Surg.* 2008;95:195–198.
40. Fass R, Fullerton S, Naliboff B, et al. Sexual dysfunction in patients with irritable bowel syndrome and non-ulcer dyspepsia. *Digestion.* 1998;59:79–85.
41. Jung H, Choung RS, Locke GR, et al. Diarrhea-predominant irritable bowel syndrome is associated with diverticular disease: a population-based study. *Am J Gastroenterol.* 2010;105:652–661.
42. Cohen E, Fuller G, Bolus R, et al. Increased risk for irritable bowel syndrome after acute diverticulitis. *Clin Gastroenterol Hepatol.* 2013;11:1614–1619.
43. Nakaji S, Danjo K, Munakata A, et al. Comparison of etiology of right-sided diverticula in Japan with that of left-sided diverticula in the west. *Int J Colorectal Dis.* 2002;17:365–373.