의학석사 학위논문

염증성 장질환 환자에서 체질량지수에 따른 임상양상 및 예후 차이에 대한 연구

The clinical features and prognosis of inflammatory bowel disease in patients with obesity

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Abstract

Background and Aims: The prevalence of obesity is increasing globally, and the prevalence of inflammatory bowel disease (IBD) is also rising. The association between IBD and obesity is controversial. Therefore, we sought to evaluate the characteristics and prognosis of IBD in obese patients.

Methods: We retrospectively reviewed the medical records of IBD patients who visited and followed up at the Asan Medical center using a large, well-characterized referral center-based cohort. The clinical features of IBD patients with body mass index (BMI) over 30 were compared with matched controls with BMI under 30.

Results: Among the 6803 IBD patients enrolled in the Asan IBD Registry between June 1989 and December 2016, we identified 16 patients with CD and 27 patients with UC whose BMI were over 30 at the time of diagnosis. Their clinical characteristics and course were compared with 64 matched patients with CD and 108 matched patients with UC, respectively. There were no significant differences in the risk of using steroids (HR 0.633, P=0.254), immunomodulators (HR 0.831, P=0.517), anti-tumor necrosis factor (TNF) therapy (HR 1.539, P=0.351), and bowel resections (HR 1.858, P=0.231) between CD patients with BMI over 30 and those with BMI under 30. UC patients also did not show significant differences in the risk of using steroids (HR 0.613, P=0.145), immunomodulators (HR 0.492, P=0.111), anti-TNF therapy (HR 0.385, P=0.095), and colectomies (HR 0.262, P=0.104).

Conclusions: Obese IBD patients, both CD and UC, did not show significantly different clinical features and prognosis compared with IBD patients with BMI under 30, respectively.

Keywords: Obesity; Inflammatory bowel disease; Clinical features; Prognosis

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Introduction

Inflammatory bowel disease (IBD) is a group of diseases in which abnormal chronic inflammation in the intestine repeats improvement and recurrence, including Crohn's disease and ulcerative colitis (UC). They are chronic debilitating disorders requiring lifelong medical treatment and often also surgery. The pathogenesis of IBD is not fully understood but is thought to be multifactorial and involve variations in the patient's genome, environmental factors, and alterations in the intestinal microbiota and the mucosal immune response.[1]

Obesity has become an important global public health issue of current era. According to the World Health Organization's data, the prevalence of overweight or obese individuals (BMI > 25 kg/m^2) is as much as 35% of the global population, and it's increasing over time.[2] The proportion of overweight adults has increased 28% in developed countries and nearly 60% in developing countries from 1980 to 2013. Globally, the cost of treating obesity and its related health complications may be as much as $2 trillion (US).[3]

The prevalence of IBD is also rising worldwide. Although IBD is usually associated with malnutrition and cachexia, the increasing global incidence of IBD and obesity has led to the hypothesis that obesity may play a role in the causes of IBD. Understanding the interaction between obesity and IBD regarding disease pathogenesis, phenotypic disease expression and response to therapy is expected to have importance in management.

There are relatively few studies which have investigated the clinical relevance of obesity and IBD, and most studies were focused on CD. In some studies, obesity was relevant to more frequent perianal complications of CD and higher rates of relapses and hospitalization,[4] as well as earlier time to loss of response to anti-tumor necrosis factor (TNF) agents.[5] Other studies showed contradictory results and obesity was even associated with a better prognosis in IBD including less anti-TNF treatment, surgery and hospitalization.[6] As such, the association between obesity and the features and course of IBD is controversial.

Especially, there are very few studies on the clinical characteristics and prognosis of obese patients with IBD in Korean populations. In this study, we aimed to describe the clinical

course of Korean IBD patients with obesity, and to compare these patients with a matched cohort.

Patients and Methods

1. Patients

Medical records of patients enrolled in the Asan IBD registry between June 1989 and December 2016 were retrospectively reviewed. Asan IBD registry is a well-characterized referral center-based cohort of Koreans with IBD,[7,8] and includes IBD patients diagnosed and treated at Asan Medical Center. The diagnostic criteria of CD and UC in this study were based on the conventional clinical, radiologic, endoscopic, and histopathologic criteria, as described previously.[9-11] Patients with age under 17, and those who were diagnosed with IBD before 1998 were excluded from this study.

To perform a matched case-control study, we defined cases and controls as follows: Cases were defined as IBD patients with BMI over 30 at diagnosis; controls were patients with BMI under 30 at diagnosis. According to Korean Society for the Study of Obesity, BMI 30 is classified as stage 2 obesity. The reason for setting the cutline at stage 2 obesity was because there were too many patients with stage 1 obesity to proceed with the study and for the purpose of getting clearer results. The Asan IBD registry consisted of 6803 IBD patients. Among the cohort, 6127 patients had BMI data. Then we isolated 311 patients whose BMI was over 30. Of that 311 patients, only 43 patients had BMI measured within 6 months of diagnosis. Controls were matched to cases with a ratio of 4:1 for disease (type of IBD), sex, calendar year of diagnosis of IBD (±2 y), and age at diagnosis of IBD (±2.5 y). The study protocol was approved by the Institutional Review Board of the Asan Medical Center.

2. Methods

Data obtained from medical records were analyzed retrospectively. For comparing the clinical features and prognosis of the patients, the sex, age, the year at diagnosis of IBD, smoking status, and extent of IBD at diagnosis were retrieved. Then we compared the clinical features and prognosis of the patients, by calculating cumulative probabilities of the use of medications (steroids, immunomodulators, anti-TNF agents) and bowel resection.

3. Statistical analysis

Continuous variables were expressed as medians with ranges. Discrete data were tabulated as numbers and percentages. Categorical data were compared between cases and controls using the chi-squared test or Fisher's exact test, where appropriate. Continuous variables were compared using the Student's t-test or the Mann-Whitney U test. Cumulative probabilities of the used of medications and surgery were calculated using the Kaplan–Meier method. Comparison between cases and matched control patients was performed using the Cox proportional hazards regression. Statistical analyses were performed using SPSS (version25.0; SPSS Inc., Chicago, IL). P-value <0.05 was considered to be statistically significant.

4. Ethical considerations

The Institutional Review Board of the Asan Medical Center approved the study protocol.

Results

1. Patient characteristics

Among the 6803 IBD patients (3171 with CD and 3632 with UC) enrolled in the Asan IBD Registry between June 1989 and December 2016, we identified 16 patients with CD and 27 patients with UC whose BMI were over 30 at the time of diagnosis.

The clinical characteristics of the IBD patients according to the Montreal Classification are shown in Table 1 and Table 2. Of the 16 obese CD patients, the number of males was 11 (68.8%) and the median age at diagnosis of CD was 21.3 years (range, 17.9 to 34.8 y). Median interval from onset to diagnosis was 9.4 months (range, 0 to 117.7 mo) and median follow-up after diagnosis of IBD was 102.1 months. The number of current, ex, never-smokers were 5 (31.3%), 1 (6.3%), 10 (62.5%) respectively. All obese CD patients (100%) were treated with corticosteroids, 7 (43.8%) with immunomodulators, and 8 (50%) were treated with anti-TNF agents. Seven patients (43.8%) received bowel resection.

In UC patients, the number of males was 21(77.8%) and the median age at diagnosis was 24 years (range, 16 to 69 y). Median interval from onset to diagnosis was 2.1 months (range, 0 to 24.7 mo) and median follow-up after diagnosis of IBD was 71.0 months. The number of current, ex, never-smokers were 7 (25.9%), 7 (25.9%), 13 (48.1%) respectively. A total of 8 patients (29.6%) were treated with corticosteroids, 3 (11.1%) with immunomodulators, and 1 (3.7%) were treated with anti-TNF agents. None of the patients received bowel resection.

Their clinical characteristics and course were compared with 64 matched patients with CD and 108 matched patients with UC. The median BMI at diagnosis of CD patients with BMI over 30 and under 30 were 31.8 and 19.1, respectively. The median BMI at diagnosis of UC patients with BMI over 30 and under 30 were 31.3 and 22.9, respectively. There were no significant differences between the obese and non-obese groups with respect to age at diagnosis, sex, smoking status, disease location and behaviors.

TABLE 1. Demographic and Clinical Characteristics of Obese and Non-obese patients with Crohn's disease

	Crohn's disease (BMI>30)	**Crohn's disease (BMI<30)**	**P-value**
No. of patients	16	64	
Median BMI at diagnosis (range)	31.8 (30.1-41.5)	19.1 (14.5-29.3)	
Male (%)	11 (68.8)	44 (68.8)	1.000[a]
Median age at diagnosis (range), yr	21.3 (17.9-34.8)	21.2 (17.9-35.9)	0.957[c]
Median interval from onset to diagnosis (range), mo	9.4 (0.0-117.7)	9.5 (0.1-108.2)	0.995[c]
Mean follow-up after diagnosis of IBD (months)	102.1±58.4	91.0±48.6	0.435[d]
Smoking status at diagnosis (%)			0.517[b]
Current smokers	5 (31.3)	20 (31.3)	
Ex-smokers	1 (6.3)	1 (1.6)	
Never-smokers	10 (62.5)	43 (67.2)	
Disease location at diagnosis (Montreal classification)			0.712[b]
L1 (Terminal ileum)	5 (31.3)	14 (21.9)	
L2 (Colon)	1 (6.3)	4 (6.3)	
L3 (Ileocolon)	10 (62.5)	46 (71.9)	
L4 (Upper GI modifier)	4 (25.0)	16 (25.0)	1.000[b]
Disease location, final (Montreal classification)			1.000[b]
L1 (Terminal ileum)	4 (25.0)	14 (21.9)	
L2 (Colon)	0 (0.0)	3 (4.7)	
L3 (Ileocolon)	12 (75.0)	47 (73.4)	
L4 (Upper GI modifier)	4 (25.0)	18 (28.1)	1.000[b]

Perianal fistula			0.592[a]
At diagnosis	8 (50.0)	24 (37.5)	
Occurrence during follow up	1 (6.3)	8 (12.5)	
Never	7 (43.8)	32 (50.0)	
Disease behavior at diagnosis (Montreal classification)			1.000[b]
B1 (Nonstricturing, nonpenetrating)	13 (81.3)	48 (75.0)	
B2 (Stricturing)	1 (6.25)	5 (7.8)	
B3 (Penetrating)	2 (12.5)	11 (17.2)	
Disease behavior, final (Montreal classification)			0.717[b]
B1 (Nonstricturing, nonpenetrating)	9 (56.3)	41 (64.1)	
B2 (Stricturing)	2 (12.5)	10 (15.6)	
B3 (Penetrating)	5 (31.3)	13 (20.3)	
Medication history			
Steroids	7 (43.8)	37 (57.8)	0.334[b]
Immunomodulators	16 (100.0)	57 (89.1)	0.312[a]
Anti-tumor necrosis factor therapy	8 (50.0)	21 (32.8)	0.201[a]
Surgical outcomes			
Bowel resection	7 (43.8)	18 (28.1)	0.228[a]

GI, gastrointestinal; IBD, inflammatory bowel disease; UC, ulcerative colitis; BMI, body mass index

[a]Chi-squared test.

[b]Fisher's exact test.

[c]Mann-Whitney U-test.

[d]t-test.

TABLE 2. Demographic and Clinical Characteristics of Obese and Non-obese patients with Ulcerative colitis

	Ulcerative colitis (BMI>30)	**Ulcerative colitis (BMI<30)**	**P-value**
No. of patients	27	108	
Median BMI at diagnosis (range)	31.3 (30.3-37.1)	22.9 (14.0-29.3)	
Male (%)	21 (77.8)	84 (77.8)	1.000[a]
Median age at diagnosis (range), yr	42 (16-69)	42 (16-71)	0.974[c]
Median interval from onset to diagnosis (range), mo	2.1 (0-24.7)	2.9 (0-63.8)	0.483[c]
Mean follow-up after diagnosis of IBD (months)	71.0±34.6	62.1±33.1	0.219[d]
Smoking status at diagnosis (%)			0.648[a]
Current smokers	7 (25.9)	23 (21.3)	
Ex-smokers	7 (25.9)	38 (35.2)	
Never-smokers	13 (48.1)	47 (43.5)	
UC extent (at diagnosis)			0.883[a]
Proctitis	12 (44.4)	52 (48.1)	
Left-sided colitis	8 (29.6)	27 (25.0)	
Extensive colitis	7 (25.9)	29 (26.9)	
UC extent (ever-worst)			0.467[a]
Proctitis	10 (37.0)	42 (38.9)	
Left-sided colitis	10 (37.0)	28 (25.9)	
Extensive colitis	7 (25.9)	38 (35.2)	
Medication history			
Steroids	8 (29.6)	49 (45.4)	0.139[a]

Immunomodulators	3 (11.1)	28 (25.9)	0.102[a]
Anti-tumor necrosis factor therapy	1 (3.7)	17 (15.7)	0.083[b]
Surgical outcomes			
Colectomy	0 (0.0)	8 (7.4)	0.159[b]

GI, gastrointestinal; IBD, inflammatory bowel disease; UC, ulcerative colitis; BMI, body mass index

[a]Chi-squared test.

[b]Fisher's exact test.

[c]Mann-Whitney U-test.

[d]t-test.

2. Clinical outcomes

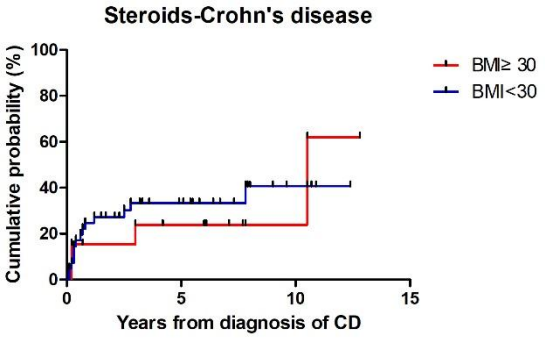
The cumulative probabilities of the need for steroid, immunomodulators, anti-TNF agents and bowel resection of CD and UC patients are presented in Figure 1 and 2.

For CD patients with BMI over 30, the cumulative probabilities of steroids use at 1, 5, 10 years after diagnosis were 31.3%, 38.1%, 69.0%, compared to 53.3%, 57.2%, 61.9%, respectively for those with BMI under 30. For CD patients with BMI over 30, the cumulative probabilities of immunomodulators use at 1, 5, 10 years after diagnosis were 43.7%, 87.5%, 93.7%, compared to 69.4%, 90.3%, 90.3% respectively for those with BMI under 30. For CD patients with BMI over 30, the cumulative probabilities of Anti-TNF use at 1, 5, 10 years after diagnosis were 19.2%, 42.9%, 54.3%, compared to 15.7%, 28.4%, 30.6%, respectively for those with BMI under 30. For CD patients with BMI over 30, the cumulative probabilities of bowel resection at 1, 5, 10 years after diagnosis were 12.5%, 48.6%, 48.6%, compared to 53.3%, 57.2%, 61.9%, respectively for those with BMI under 30.

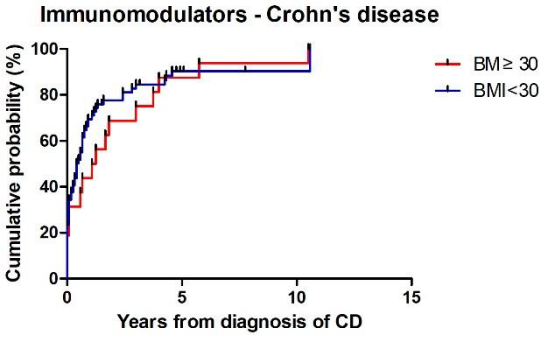
For UC patients with BMI over 30, the cumulative probabilities of steroids use at 1, 5, 10 years after diagnosis were 22.7%, 30.8%, 30.8%, compared to 37.3%, 45.4%, 59.1%, respectively for those with BMI under 30. For UC patients with BMI over 30, the cumulative probabilities of immunomodulators use at 1, 5, 10 years after diagnosis were 4.0%, 12.0%, 12.0%, compared to 9.8%, 25.8%, 28.5%, respectively for those with BMI under 30. For UC patients with BMI over 30, the cumulative probabilities of anti-TNF use at 1, 5, 10 years after diagnosis were 0%, 4.0%, 4.0%, compared to 6.8%, 18.1%, 18.1%, respectively for those with BMI under 30. For UC patients with BMI over 30, the cumulative probabilities of colectomy at 1, 5, 10 years after diagnosis were 0%, 0%, 0%, compared to 1.9%, 5.4%, 25.7%, respectively for those with BMI under 30.

There were no significant differences in the risk of using steroids (Hazard ratio [HR] 0.633; 95% confidence interval [CI] 0.289–1.388, P=0.254), immunomodulators (HR 0.831; 95% CI 2.226–3.374, P=0.517), anti-TNF therapy (HR 1.539; 95% CI 0.136–1.022, P=0.351), and bowel resections (HR 1.858; 95% CI 0.674–5.119, P=0.231) between CD patients with BMI over 30 and those with BMI under 30. In UC, patients also did not show significant differences in the risk of using steroids (HR 0.613; 95% CI 0.317–1.185, P=0.145), immunomodulators (HR 0.492; 95% CI 0.205–1.177, P=0.111), anti-TNF therapy (HR 0.385; 95% CI 0.125–1.180, P=0.095), and colectomies (HR 0.262; 95% CI, 0.052–1.319, P=0.104).

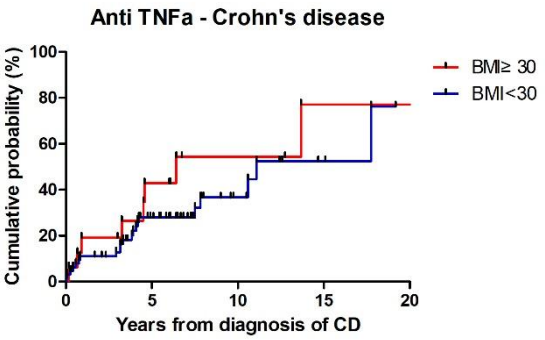
Figure 1. Cumulative probabilities of treatment – Crohn's disease



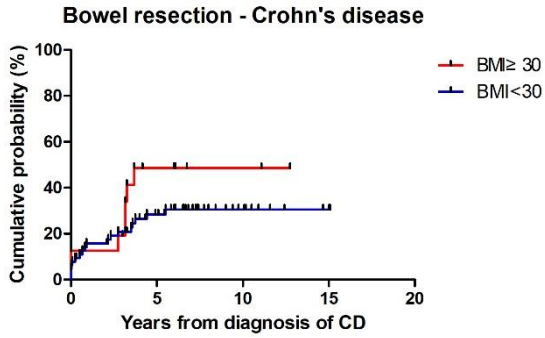
p=0.254



p=0.517

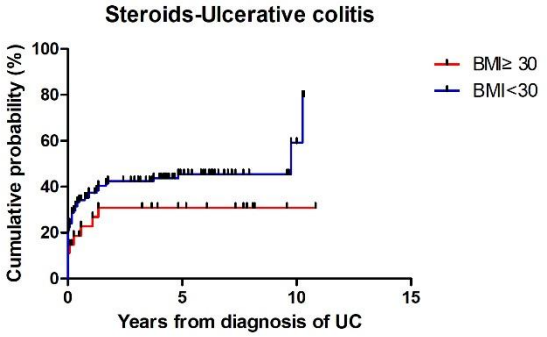


p=0.351

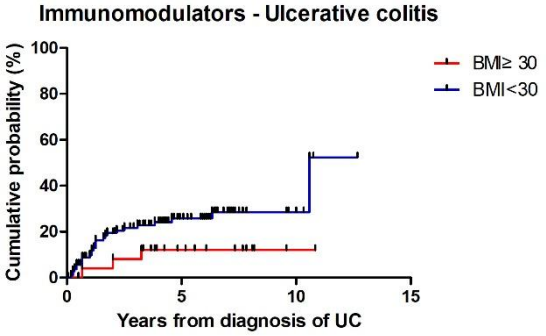


p=0.231

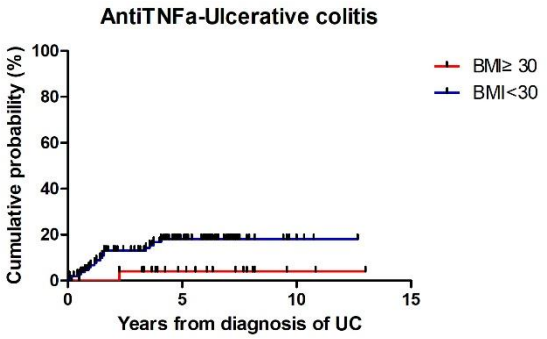
Figure 2. Cumulative probabilities of treatment – Ulcerative colitis



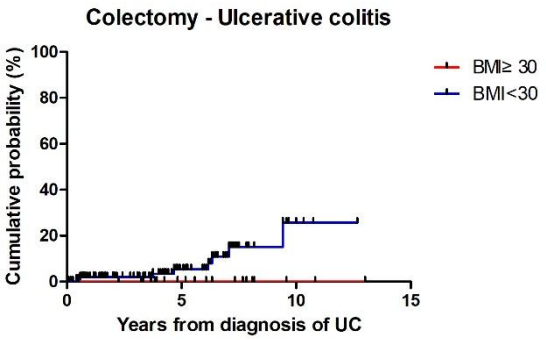
p=0.146



p=0.111



p=0.095



p=0.104

Discussion

To the best of our knowledge, this is the first study to compare the clinical features and prognosis of obese and non-obese patients with IBD by calculating cumulative probabilities of receiving treatment in Korea.

The mechanisms by which obesity contributes to IBD can be largely explained in two ways. The first one is the role of adipose tissue. There are some reasons to suspect that large amount of adipose tissue may contribute to gut inflammation. Mesenteric visceral adipose tissue has a predominance of pro-inflammatory macrophages that secrete several inflammatory cytokines.[12] In addition, adipocytes also produce other pro-inflammatory cytokines such as IL-6 and adipokines such as leptin and resistin. These pro-inflammatory cytokines and adipokines are thought to promote inflammatory responses in the gut.[13] Although overall obesity was not always associated with more severe disease activity and complications, visceral fat was independently associated with an increased risk of IBD-related complications.[14,15] In one cross-sectional study, CD patients with complications had a higher CT-measured visceral fat area and a higher visceral to subcutaneous fat area ratio compared to those without complications.[16]

Secondly, it can be explained with the role of intestinal dysbiosis. According to emerging research,[17-19] obesity induces intestinal barrier dysfunction which plays an important role in the pathogenesis of various obesity-induced diseases. Many studies have shown that obese patients have impaired intestinal barrier function, leading to enhanced translocation of bacteria or toxic bacterial products from the gut into the bloodstream and distant organs, resulting in systemic inflammation, insulin resistance, and tissue dysfunction.[17-19] This barrier dysfunction is also a key pathogenic factor in IBD as well as obesity.[20] This is the one of the reasons why obesity may have impact on IBD's clinical outcome.

The results of previous studies on the association between obesity and the clinical outcome of IBD vary, but we predicted that obesity would have negative impact on clinical outcomes and prognosis of IBD. In our study, there were no significant differences between the two groups.

Perhaps the reason is, when determining the two matching groups it would have made better comparison by matching overweight vs underweight, or overweight vs normal weight. But in this study, we compared the patients with BMI over 30 vs BMI under 30, which makes underweight patients grouped together with normal weight patients for the analysis. It may have obscured the association between obese and normal weight patients by including sicker patients in the comparator group, as low BMI could reflect disease activity of IBD patients.[21]

Another reason can be explained like this. A low BMI may be the result rather than the cause of IBD activity and that obesity is merely a reflection of less aggressive or less severe IBD. This is supported by the findings of a recent study from Ireland, which found that obese or overweight patients with CD had an overall less aggressive disease course.[22]

Thirdly, the association between obesity and IBD got attention as global prevalence of obesity and IBD increased. However, the increase in prevalence of IBD in Western countries has not been as dramatic as the increase in prevalence of obesity. This may suggest that the increase in the frequency of obesity in IBD patients merely reflects the rising frequency of obesity in the general population and that obesity is not contributing to the pathogenesis of IBD. To support this, a recent European epidemiologic study has found no significant association between obesity and the development of IBD.[23]

Our study has several limitations. The first limitation was explained previously, that underweight and normal weight patients were both included in the matched groups. A second limitation of this study is its retrospective nature, which selection bias cannot be eliminated. A large portion of patients were excluded due to missing data on BMI. Thus, we were only able to include 16 patients with CD and 27 patients with UC whose BMI was over 30 at the time of diagnosis. And a large proportion of patients with existing BMI data had hospitalization history. Vice versa, a lot of patients without hospitalization history did not have BMI data and were excluded from the study. Therefore, our study might have enrolled greater portion of IBD patients with worse clinical outcomes than the general IBD population, and it could have biased the results of our study. Thirdly, the study cohort included patients only from a single tertiary referral center, which may cause referral bias. Also, due to the study's small sample size, the results need to be interpreted cautiously. Thus, we performed 1:4 case–control matching analysis to improve the statistical power of

the study. Finally, BMI is not a perfect measure of degree of obesity, as the effect of obesity on our body is theoretically thought as the effect of adipose tissue in our body. Other measures which can measure the degree of obesity(adipose tissue) includes waist circumference, waist-hip ratio, and visceral fat measurement by cross-sectional imaging etc.[24,25] Future studies should explore the relationship of BMI to visceral fat as measured by anthropometric measurements or imaging, or better still, the impact of visceral fat alone in CD and UC.

In conclusion, there were no significant differences in prognosis represented by cumulative probabilities of receiving treatment between the obese and non-obese patients with IBD. Further prospective, long-term follow-up studies are needed to confirm these observations.

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국문요약

배경: 비만의 유병률은 전 세계적으로 증가하고 있으며 염증성장질환의 유병률 또한 증가하고 있다. 염증성장질환은 일반적으로 영양실조 및 악액질과 관련이 있지만 비만과의 관련성은 여전히 논란의 여지가 있다. 따라서 우리는 비만 환자에서 염증성장질환의 특성과 예후를 평가하고자 하였다.

연구방법: 서울아산병원에서 진료를 보고 추적한 IBD 환자 코호트 기록을 후향적으로 검토했다. 체질량 지수가 30 이상인 IBD 환자와 BMI 가 30 미만인 IBD 대조군의 임상양상과 예후를 비교하였다.

결과: 1989 년 6 월부터 2016 년 12 월까지 서울아산병원 IBD 코호트에 등록된 6803 명의 IBD 환자[크론병 3171 명 및 궤양성 대장염 3632 명] 중 진단 시 BMI 가 30 이상인 크론병 환자 16 명과 UC 환자 27 명을 선별하였다. 그들의 임상적 특징과 경과를 1:4 로 짝지어진 64 명의 크론병 환자와 108 명의 궤양성 대장염 환자와 비교하였다. BMI 30 이상과 30 이하의 크론병 환자들에서 스테로이드(HR 0.633; 95% CI 0.289–1.388, P=0.254), 면역조절제(HR 0.831; 95% confidence interval [CI] 2.226–3.374, P=0.517), 항-TNF 제제(HR 1.539; 95% CI 0.136–1.022, P=0.351) 사용 및 장절제술(HR 1.858; 95% CI 0.674–5.119, P=0.231)의 위험률에는 유의한 차이가 없었다. UC 환자에서도 BMI 30 이상과 30 이하 군 간의 스테로이드(HR 0.613; 95% CI 0.317–1.185, P=0.145), 면역조절제(HR 0.492; 95% CI 0.205–1.177, P=0.111), 항-TNF 제제(HR 0.385; 95% CI 0.125–1.180, P=0.095)의 사용 및 장 절제술(HR 0.262; 95% CI,0.052–1.319, P=0.104)의 위험률에는 유의한 차이가 없었다.

결론: 비만한 염증성장질환 환자의 임상양상 및 예후는 체질량 지수 30 이하의 염증성장질환 환자와 비교하여 유의한 차이가 나지 않았다.

중심단어: 비만; 염증성 장질환; 임상양상; 예후