의학석사 학위논문

Significance of Plasma Ghrelin and Leptin Level as Surrogate Markers for Intestinal Inflammation in Patients with Crohn's Disease

크론병 환자에서 장내 염증 상태를 나타내는 대리 표지자로서 혈중 그렐린과 렙틴 농도의 유용성

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장 승 현

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Significance of Plasma Ghrelin and Leptin Level as Surrogate Markers for Intestinal Inflammation in Patients with Crohn's Disease

by

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Professor _____Chairman

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ABSTRACT

Introduction: The most important determinant of the clinical course of Crohn's disease (CD) is the balance of proinflammatory, anti-inflammatory, and immunomodulating factors. Determining inflammatory activity is crucial for the assessment of disease activity and for the tailoring of therapy. Inflammatory reactions localized in the bowel wall may penetrate the surrounding visceral adipose tissue. Activated visceral adipocytes secrete many mediators, such as leptin, adiponectin, and ghrelin. The present study was designed to evaluate fasting serum levels of leptin, adiponectin, obestatin, and ghrelin in CD patients, and determine whether theses markers can be surrogate markers for intestinal inflammation and disease activity in CD patients.

Methods: From march 2009 to February 2012, we collected serum samples and analyzed the clinical features of CD patient at thirteen hospitals nationwide in Korea. Fasting leptin, adiponectin, obsestatin, and ghrelin concentrations were measured using commercially available enzyme-linked

immunosorbent assay. The patients were classified on the basis of the Montreal classification and medical records were collected retrospectively. We analyzed relationship between serum adiopcytokine levels and clinical parameters of CD patients.

Results: One hundred and fifty-three CD patients were included. Serum ghrelin level was negatively correlated with patient's age ($p=0.041$) and age at diagnosis ($p=0.017$), and positively correlated with CRP level ($p=0.017$) with statistically significance in univariate analysis. In multivariate analysis, serum ghrelin level was correlated statistically significant only with CRP level ($p=0.032$). Serum leptin level was also correlated with CRP level ($p<0.001$). The adipocytokine levels were not significantly different according to the disease location nor behavior. Serum ghrelin level was lower in surgery group than non-surgery group with statistically significant ($p=0.007$).

Conclusions: Our analysis showed that serum leptin and ghrelin levels can be a potential surrogate inflammatory marker for CD, and may serve as useful tools to estimate disease activity in

clinical practice.

Keywords: Leptin, Crhon's disease, Disease activity, Inflammation

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LIST OF ABBREVIATIONS

IBD, inflammatory bowel disease

CD, Crohn's disease

CRP, C-reactive protein

SD, standard deviation

CDAI, Crohn's disease activity index

BMI, body mass index

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disorder that can affect entire gastrointestinal tract, and it occurs frequently in the small intestine and colon. Although genetic, immunological and environmental factors have been proposed, the mechanism remains unclear. Patients with CD go through repeated periods of aggravation and improvement during the course of disease and many patients eventually require operations due to structuring or penetrating complications(1). Although higher incidences and prevalences of CD have been reported in Western countries, recent studies have shown gradually increasing incidences and prevalences in Asian countries, including Korea(2). The most important determinant of the clinical course of CD is the balance, levels, and ratios of proinflammatory, anti-inflammatory, and immunomodulating factors. Determining the presence of intestinal inflammation is a primary criterion for the diagnosis CD as well as for the differentiation from other diseases. Determining inflammatory activity is crucial for the assessment of disease activity and for the tailoring of therapy(3).

The incidence of CD has been shown to be related to dietary intake of total fat, suggesting that CD is a lifestyle-related disease(4). Inflammatory reactions localized in the bowel wall may penetrate the surrounding visceral adipose tissue. The anatomic proximity of the bowel and visceral fat favors the activation of adipocytes. Activated visceral adipocytes secrete many mediators, such as leptin, adiponectin, and ghrelin(5). Anorexia, malnutrition, altered body composition, and development of mesenteric obesity, are well-known features of CD, indicating an important role for white adipose tissue-secreted proteins(6). It is suggested that these adipocytokines may participate in the disease pathogenesis(7).

Ghrelin is an endogenous ligand of the growth hormone secretagogue receptor, and was first reported in 1999. Ghrelin has a crucial role in the regulation of food intake and energy homeostasis(8). It is mainly produced at the stomach but is also expressed in adipose tissue(9). Recently, high circulating ghrelin levels have been found in patients with celiac disease and active inflammatory bowel disease (IBD)(10, 11). Obestatin derived from the same proprotein with ghrelin but act through distinct receptors(12). In contrast to ghrelin, which causes

hyperphagia and obesity, obestatin appears to act as a counter-regulatory hormone by decreasing food intake, gastric emptying activities, jejunal motility, and body-weight gain(12). There is lack of studies about the role of serum obestatin and obestatin/ghrelin ratio in disease activity of IBD. Leptin and adiponectin are another adipocytokines. In a previous study to evaluate the change in circulating levels of leptin and adiponectin after induction therapy of patients with active IBD, it showed no significant alterations in serum levels of leptin and adiponectin after induction therapy(13).

C-reactive protein (CRP) is a marker of inflammation, and serum CRP concentration reflects disease activity in patients with CD(14, 15). CRP has a short half-life and consequently it is early after the onset of the inflammatory process and rapidly decreases after its resolution making it an attractive marker of disease activity(16). Moreover, it is inexpensive and easy to perform and is unaffected by medication. But clinical usefulness as a disease activity marker of CRP levels are dependent on disease location(17) .

The present study was designed to evaluate fasting serum levels of leptin, adiponectin, obestatin, and ghrelin in CD

patients, to correlate the results with the disease activity and the clinical characteristics of the disease, and to examine the possible interaction between the estimated hormone values. So we can determine whether theses hormones can be potential surrogate markers for intestinal inflammation and disease activity in CD patients.

MATERIALS AND METHODS

1. Patients

From march 2009 to February 2012, we collected serum samples and analyzed the clinical features of CD patient at thirteen hospitals nationwide in Korea. Among the patients those who had well characterized clinical manifestations and disease duration of at least 2 years were enrolled this study. Serum samples were collected at outpatient departments from enrolled patient. The diagnosis of CD was based on clinical, endoscopic, histologic, and radiographic results(18). Disease activity in CD patients was evaluated with the CD activity index (CDAI)score (19). The patients were classified on the basis of the Montreal classification (age at diagnosis, disease location, disease behavior)(20). Medical records including demographic data, laboratory data, endoscopic findings, medication history, history of abdominal surgery and presence of perianal involvement were collected retrospectively. This study was approved by institutional review board at Seoul National University Boramae Hospital (IRB No. 06-2010-170) and was

conducted according to the Declaration of Helsinki.

2. Assessment of serum adiopcytokine concentrations

All blood samples were collected at the time of registration in the 30 minute before breakfast after overnight fast longer than 12 hours. Whole blood was directily withdrawn and stored in centrifuge tube that contained 500U of aprotinin and 1.25 mg of EDTA-2Na per 1 ml of whole blood. The blood samples were immediately centrifuged at 1,500 X g for 15 min at 4° C. Plasma samples were acidified with 100 μl of 1 mol/l HCl per ml of collected plasma and stored at -70° C until assayed. Withdrawn blood samples were sent to central clinical laboratory. Leptin, adiponectin, obsestatin, and ghrelin concentrations were measured using commercially available enzyme-linked immunosorbent assay(ELISA) kits (leptin: R&D Systems, Abington, UK; ghrelin, andiponectin, and obestatin: LINCO Research, Missouri, USA). To avoid laboratory error, serum adipocytokine concnetrations were mesured by triplet seperately.

3. Comparison adipocytokine levels and clinical parameters

We evaluated the correlation between serum adipocytokine levels and other serologic markers including erythrocyte sedimentation rate (ESR) and CRP. Other clinical features including body mass index (BMI), disease location, disease behavior, history of abdominal surgery and presence of perianal involvement were also evaluated.

4. Statistical analysis

Patient's demographics and clinical characteristics were expressed as means and as numbers (percentages). Continuous variables were expressed as mean ± standard deviation (SD) and analyzed using Student's t-test or Mann-Whitney U tests. Categorical variables were compared using the chi-squared test of Fisher's exact test. Analysis was performed using the statistical software package SPSS 18.0 (SPSS Inc., IL, Chicago). A p-value < 0.05 were considered statistically significant.

RESULTS

1. Characteristics of patients

One hundred and fifty-three CD patients were included. One hundred and twenty-four (81.0%) patients were male and mean age was 36.1 ± 10.0 years. Seventy-one (46.4%) patients underwent abdominal surgery before enrollment and sixty-four (41.8%) patient had perianal involvement. The mean duration of disease were 122.9 ± 48.3 months (Table 1). The distribution of patients according to Montreal classification are described in Table 1. Fourty-four patients (28.8%) had information for CDAI score. Patients with CDAI score less than 150 were considered to have inactive disease.

Table 1. Clinical characteristics of enrolled patients

Patients	N = 153
Age (year)	36.1 ± 10.0
Male gender	124 (81.0%)
BMI (kg/m^2)	20.6 ± 1.0
History of abdominal surgery	71 (46.4%)
Perianal involvement	64 (41.8%)
Duration of disease (months)	122.9 ± 48.3
Disease location	
Terminal ileum	19 (12.4%)
Colon	17 (11.1%)
Ileocolon	105 (68.6%)
Upper GI	1 (0.07%)
Disease behavior	
Non-stricturing non-penetrating	49 (32.0%)
Stricturing	23 (15.0%)
Penetrating	70 (45.8%)
CDAI score	44 (28.1%)
<150	19 (12.4%)
≥150	25 (16.3%)

Data were expressed as mean ± SD or number (%)

2. Summarized information of serum adipocytokine concentrations

The mean serum ghrelin and leptin level of enrolled patients were 800.12 pg/ml (range: 257−3161) and 4.07 ng/ml (range: 0.54−28.80) respectively (Table 2). The clinical features of CD patients according to ghrelin (<800 pg/ml or ≥800 pg/ml)

and leptin (<4 ng/ml or ≥4 ng/ml) concentrations are described in table 3. There were high prevalence of male gender in low ghrelin and leptin concentration group (p=0.027 and p<0.001, respectively).

Table 2. Descriptive analysis of serum adiopcytokine levels

	Mean	Minimum	Maximum	SD
Ghrelin (pg/ml)	800.12	257	3161	358.65
Leptin (ng/ml)	4.07	0.54	28.80	4.06
Adiponectin (μg/ml)	8.00	2.5	21.4	3.19
Obestatin (ng/ml)	4.38	2.57	18.32	1.56

SD, standard deviation

Table 3. Clinical characteristics of patients with CD according to ghrelin and leptin level

	Ghrelin			Leptin		
	<800 pg/ml (N=81)	≥800 pg/ml (N=72)	p value	<4 ng/ml (N=109)	≥4 ng/ml (N=44)	p value
Age (year)	37.4 ± 10.3	34.7 ± 9.5	0.089	35.7 ± 9.3	37.1 ± 11.5	0.487 [a]
Male gender	71 (87.7%)	53 (73.6%)	0.027	98 (89.9%)	26 (59.1%)	<0.001 [b]
BMI	20.7 ± 1.0	20.6 ± 0.9	0.505	20.7 ± 1.0	20.4 ± 1.0	0.178 [a]
History of abdominal surgery	42 (51.9%)	29 (40.3%)	0.152	50 (45.9%)	21 (47.8%)	0.835 [b]
Perianal involvement	31 (38.3%)	33 (45.8%)	0.344	49 (45.0%)	15 (34.1%)	0.218 [b]
Duration of disease (months)	120.9 ± 47.0	125.1 ± 49.9	0.597	121.5 ± 47.5	126.3 ± 50.7	0.594 [a]

Data were expressed as mean ± SD or number (%)

[a] Chi-square test

[b] Independent t-test

3. Serum adipocytokine concentrations and clinical parameters

In univariate analysis, we compared serum adipocyotkine levels to age, BMI, age at diagnosis, disease duration, serum CRP levels, serum ESR levels, and CDAI by Pearson correlation coefficient and regression(Table 4). Serum ghrelin level was negatively correlated with patient's age (p=0.041) and age at diagnosis (p=0.017) and positively correlated with CRP level (p=0.017) with statistically significance in univariate analysis. Ghrelin concentration was not significantly different according to BMI (p=0.179), disease duration (p=0.482), ESR (p=0.853) and CDAI (p=0.439). We performed multivariate analysis for significant variables in univariate analysis by multiple regression analysis. In multivariate analysis, serum ghrelin level was correlated statistically significant only with CRP level (p=0.032) (Table 5, Figure 1). Serum leptin level was also correlated with CRP level (p<0.001)(Figure 2). But serum obestatin level and obestatin/ghrelin ratio were not significantly correlated with CRP level (p=0.743 and p=0.145 respectively).

Table 4. Univariate analysis of the association between serum adiopcytokine levels and various parameters in CD patients

	Ghrelin		Leptin		Adiponectin		Obestatin	
	r-value	p-value	r-value	p-value	r-value	p-value	r-value	p-value
Age	-0.166	0.041	0.038	0.637	0.087	0.284	0.051	0.533
BMI	-0.109	0.179	-0.085	0.296	-0.078	0.336	0.083	0.309
Age at diagnosis	-0.193	0.017	-0.066	0.416	0.064	0.431	0.048	0.553
Disease duration	0.057	0.482	-0.043	0.595	0.077	0.345	-0.009	0.909
CRP	0.245	0.017	0.373	<0.001	-0.077	0.461	-0.034	0.743
ESR	0.020	0.853	-0.033	0.756	-0.127	0.405	-0.036	0.735
CDAI	-0.118	0.439	-0.201	0.186	-0.002	0.982	0.269	0.074

r, Pearson correlation coefficient

Table 5. Multivariate analysis for serum ghrelin level

	β-value	95% CI	p-value
Age	-0.331	-25.317 ~ 7.769	0.295
Age at diagnosis	0.124	-13.533 ~ 20.230	0.695
CRP	0.219	0.719 ~ 15.842	0.032

CI, confidential interval

β-value, standardized coefficient

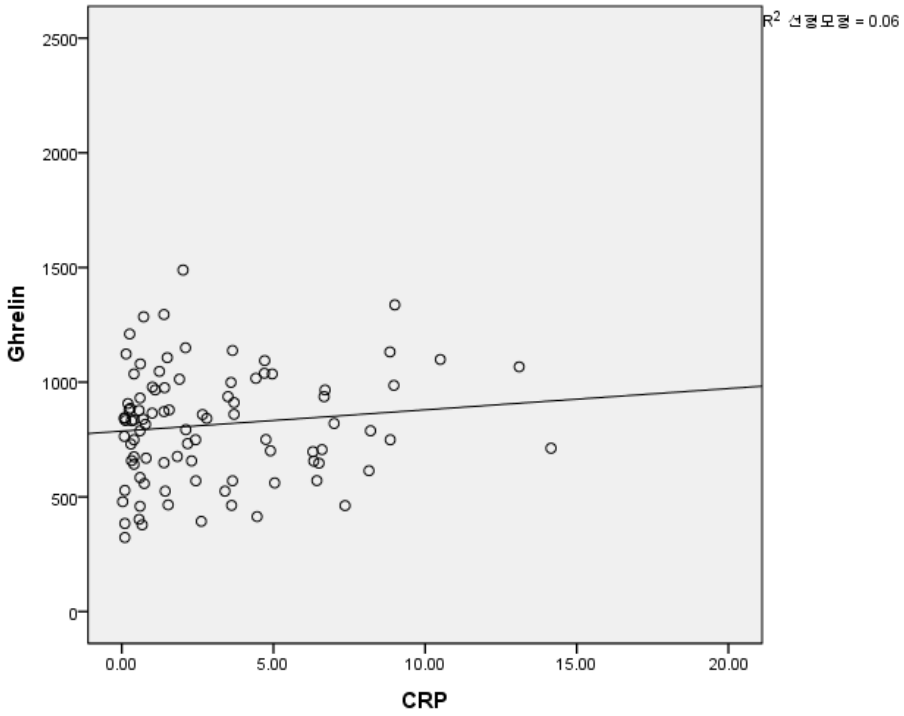


Figure 1. Simple linear regression analysis between serum ghrelin concentration and CRP level. The mean serum ghrelin concentrations showed correlation with CRP levels (p=0.032) in patients with CD.

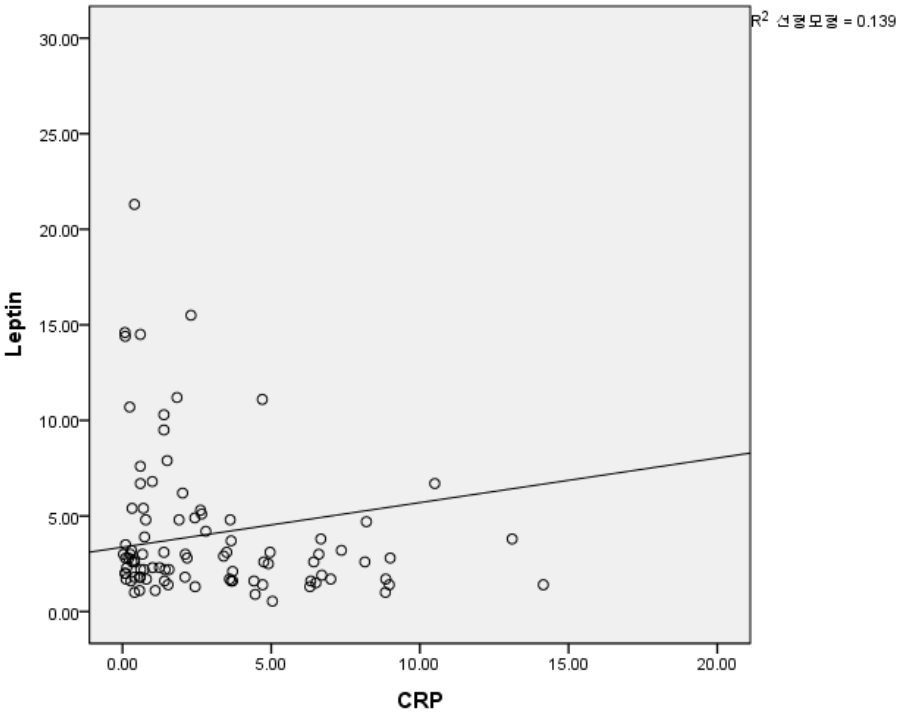


Figure 2. Simple linear regression analysis between serum leptin concentration and CRP level. The mean leptin concentrations showed correlation with CRP levels ($p<0.001$) in patients with CD.

4. Serum adipocytokine concentrations and CDAI score

We could calculate CDAI score at the time of data collection of fourty-four (28.8%) patients. Patients with CDAI score above 150 considered to have an active disease. Seurm adipocytokine levels of CD patients according to CDAI score (CDAI < 150 or CDAI ≥ 150) are described in Table 6. There were no statistically significant deference of serum adipocytokines between active and inactive CD patients.

Table 6. Serum adipocytokine levels of CD patients according to CDAI score

	CDAI <150 (N=19)	CDAI ≥150 (N=25)	P value
Ghrelin (pg/ml)	866.21 ± 347.80	755.96 ± 199.25	0.574
Leptin (ng/ml)	6.64 ± 5.58	4.07 ± 4.47	0.089
Adiponectin (μg/ml)	8.85 ± 3.74	7.57 ± 3.30	0.384
Obestatin (ng/ml)	4.15 ± 0.87	4.43 ± 1.68	0.826

Data were expressed as mean ± SD

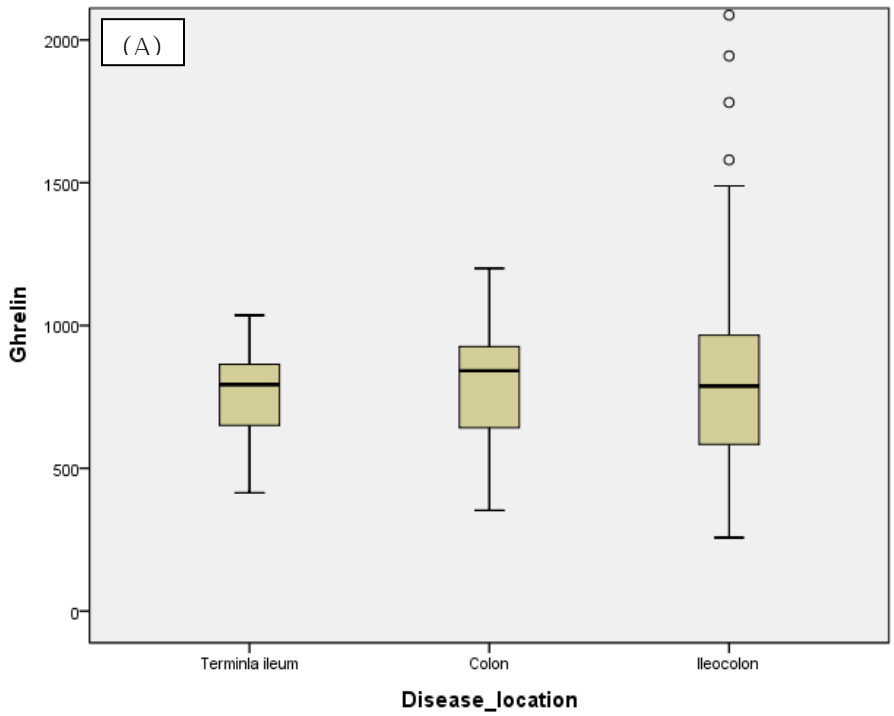
5. Serum adipocytokine levels and disease behavior or disease location of Crohn's disease

The patients were categorized by disease location (ileum, colon, ileocolon) and disease behavior (non-stricturing non-penetrating, stricturing, penetrating) according to the Montreal classification at the time of diagnosis. We performed one-way ANOVA test separately for across the different disease location and behavior. And we reclassified disease location simply to isolated ileal disease (N=20, 13.1%) and disease involved colon (N=122, 79.7%). The adipocytokine levels were not significantly different according to the disease location (Table 7, Figure 3). Also there were no significant correlation between serum adipocytokine levels and disease behavior (Figure 4). Sixty-four (41.8%) patients had perianal involvement. But there were no statistically significant difference in serum adipocytokine levels including ghrelin according to presence of perianal involvement (Table 8, Figure 5)

Table 7. Serum adipocytokine levels and disease location of CD patients

	Isolated ileal disease (N=20)	Colon involvement (N=122)	p-value
Ghrelin (pg/ml)	751.25 ± 197.70	827.15 ± 380.53	0.182
Leptin (ng/ml)	4.36 ± 4.98	4.14 ± 4.07	0.851
Adiponectin (μg/ml)	8.58 ± 3.98	7.97 ± 2.86	0.517
Obestatin (ng/ml)	4.74 ± 1.88	4.26 ± 1.53	0.290

Data were expressed as mean ± SD



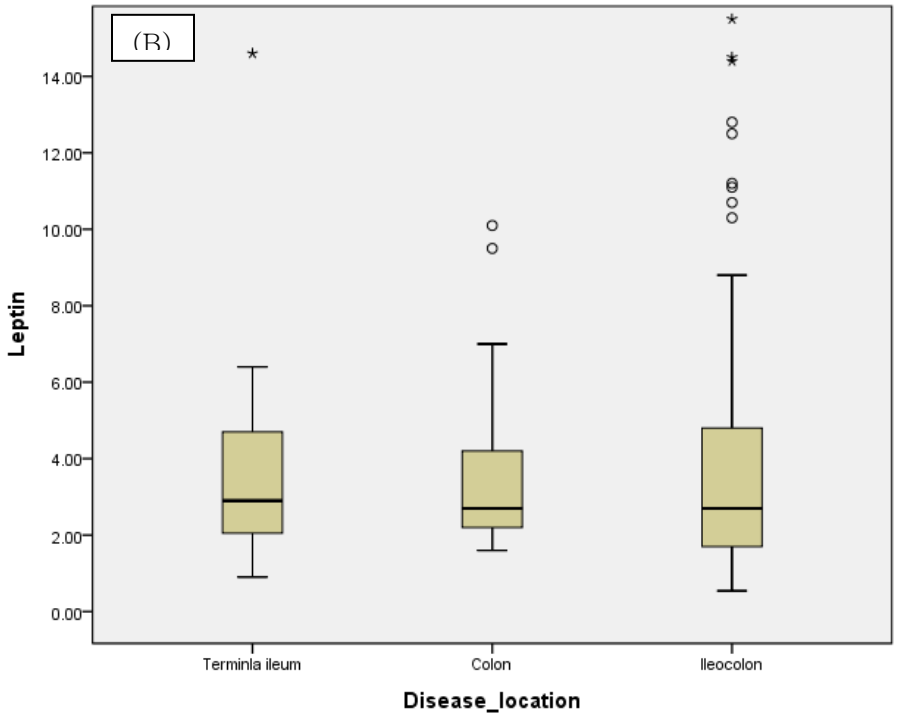
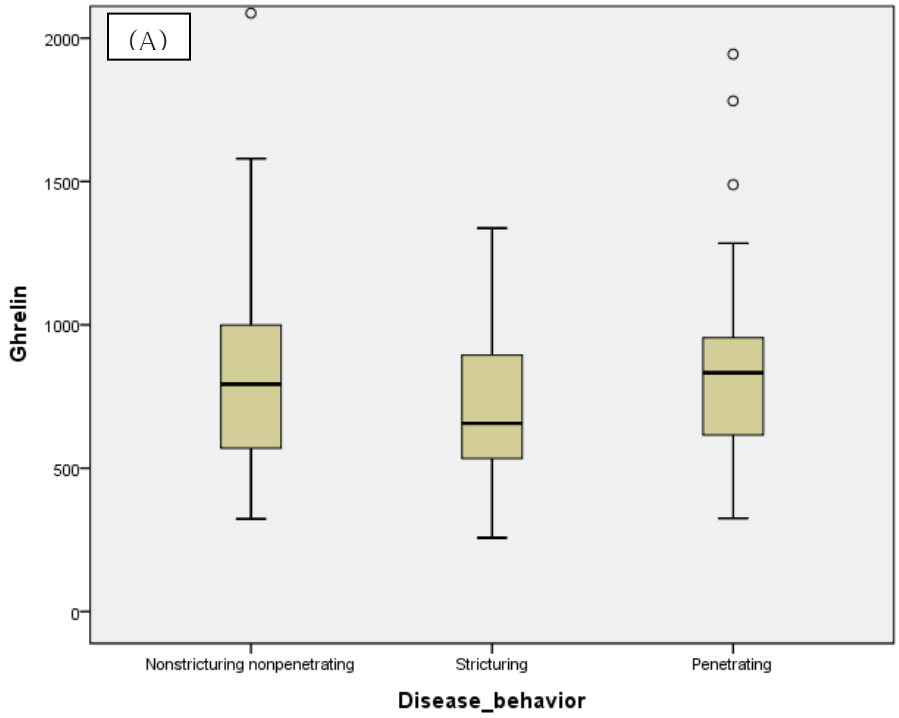


Figure 3. Serum ghrelin (A) and leptin (B) concentrations according to the disease location. Serum ghrelin and leptin concentrations showed no differences according to the disease location in patients with CD.


(A)
Ghrelin
2000
1500
1000
500
0
Nonstricturing nonpenetrating
Stricturing
Penetrating
Disease_behavior

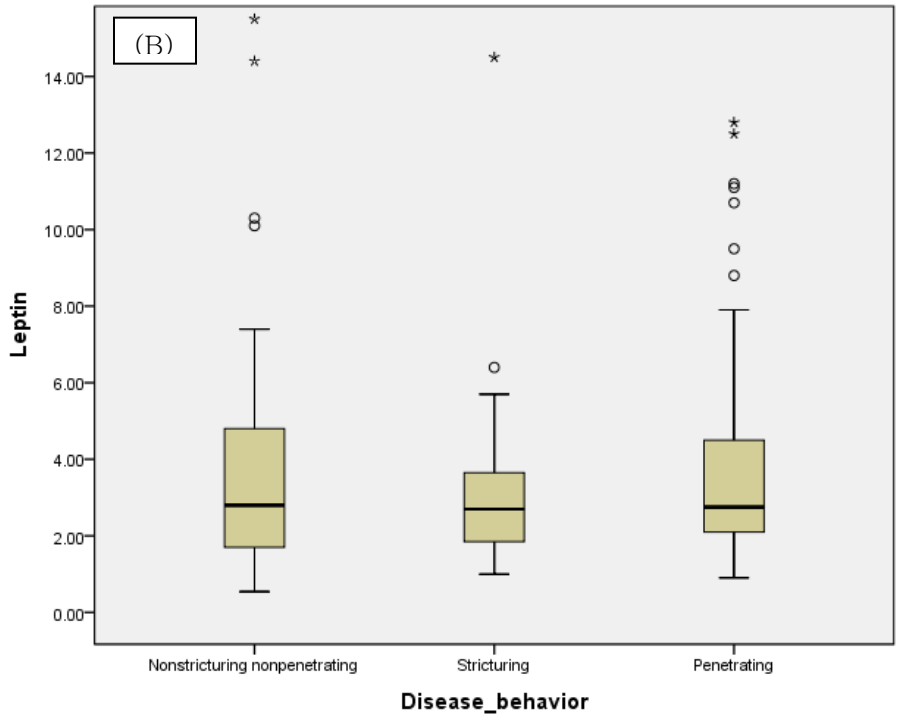

(B)
Leptin
14.00
12.00
10.00
8.00
6.00
4.00
2.00
0.00
Nonstricturing nonpenetrating
Stricturing
Penetrating
Disease_behavior

Figure 4. Serum ghrelin (A) and leptin (B) concentrations according to the disease behavior. Serum ghrelin and leptin concentrations showed no differences according to the disease behavior in patients with CD.

Table 8. Serum adipocytokine level and presence of perianal involvement in CD patients

	Perianal involvement (N=64)	No perianal involvement (N=89)	p-value
Ghrelin (pg/ml)	784.11 ± 301.94	811.63 ± 395.72	0.626
Leptin (ng/ml)	3.74 ± 4.12	4.31 ± 4.03	0.400
Adiponectin (μg/ml)	7.77 ± 3.14	8.17 ± 3.23	0.451
Obestatin (ng/ml)	4.31 ± 1.01	4.42 ± 1.87	0.400

Data were expressed as mean ± SD

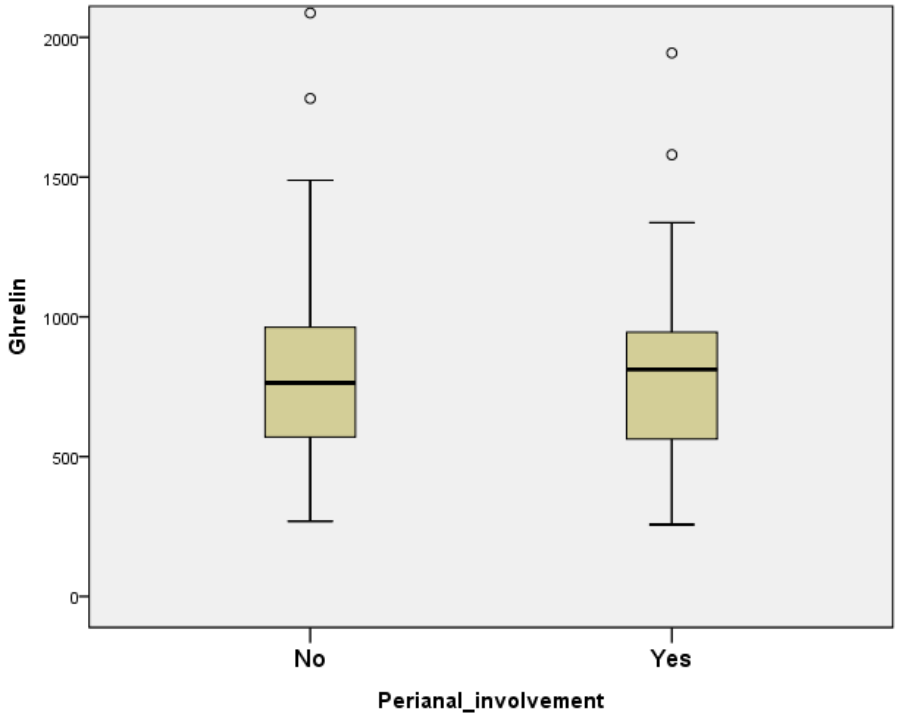


Figure 5. The mean concentrations of serum ghrelin according to presence of perianal involvement. There were no statistically significant difference in serum ghrelin levels according to presence of perianal involvement (p=0.626) in patient with CD

6. Association between serum ghrelin and surgical history

Of 153 patients, seventy-one (46.4%) patients had been underwent abdominal surgery at the time of data collection. We

compared serum adipocytokine levels between surgery group and non-surgery group by t-test. As a result, serum ghrelin level was lower in surgery group than non-surgery group with statistically significant (p=0.007)(Figure 6). But other adiopcytokines were not significantly different according to history of surgery.

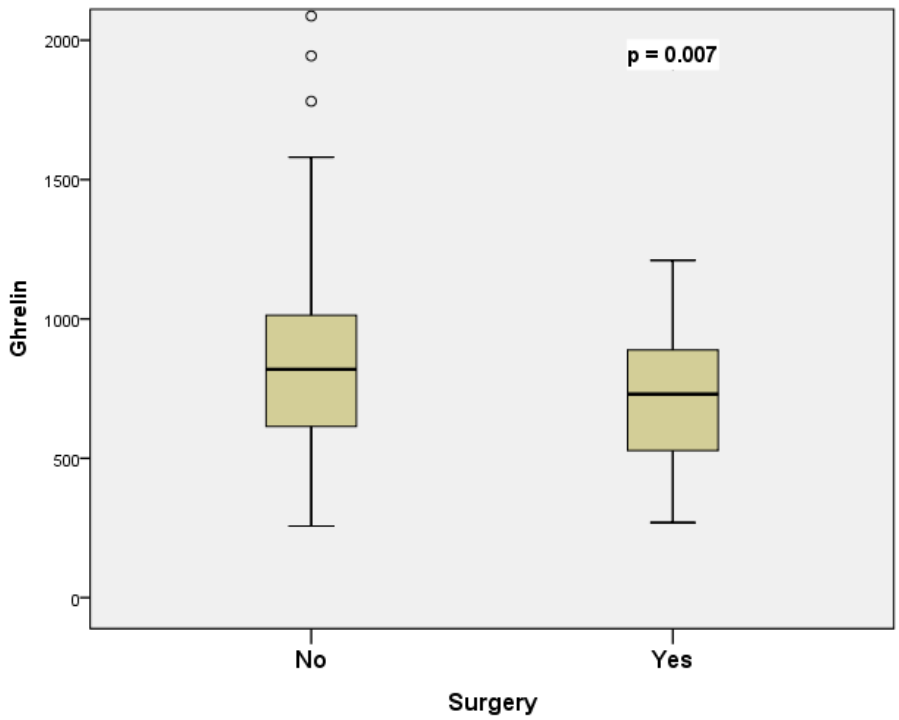


Figure 6. The mean concentrations of serum ghrelin according to history of abdominal surgery. The mean ghrelin concentrations showed significant difference according to history of abdominal surgery (p=0.007) in patients with Crohn's disease.

DISCUSSION

Serum CRP concentration has been regarded as a disease activity marker of CD. A study of Mayo Clinic showed that moderate to severe clinical activity, active lesions at colonoscopy, and histologically active inflammation were significantly associated with elevated CRP level in CD patients(15). Markers other than CRP may indicate disease activity in patients with CD. For example, fecal calprotectin and lactoferrin were shown to be more sensitive predictors of endoscopically active CD than CDAI and CRP(21). In our study, we measured the circulating levels of 4 adipocytokines in patients with CD. These hormones are produced human adipose tissue, and are related to metabolism and inflammation. Inflammatory reactions localized in the bowel wall of CD patients may penetrate the surrounding visceral adipose tissue and adipose tissue can release these adipocytokines.

We compared clinical features of CD patients according to ghrelin (<800 pg/ml or ≥800 pg/ml) and leptin (<4 ng/ml or ≥4 ng/ml) concentrations. There were male predominance in both lower concentration group ($p=0.027$ for ghrelin and $p<0.001$ for

leptin, respectively). But other clinical features were not significantly different between two group. Previous reports on healthy population found that ghrelin level is higher in women than men(22). But there were no report about gender difference of ghrelin or leptin level in CD patients. This study may be the first report comparing the clinical features of CD patients between low concentration and high concentration group by serum ghrelin and leptin.

Perrachi et al. reported high serum ghrelin levels in patients with UC and CD. They found positive correlation between serum ghrelin levels and disease activity, TNF-alpha, and serum CRP levels(11). In our study, it was found that there were significant correlation between serum ghrelin level and CRP ($p=0.032$). This finding suggests that serum ghrelin can be a potential surrogate marker of intestinal inflammation for CD patients. Obestatin is a peptide hormone derived from the same gene that encodes ghrelin(12). There was lack of studies about the role of serum obestatin and obestatin/ghrelin ratio in disease activity of IBD. So we performed analysis for serum obestatin and obestatin/ghrelin ratio comparing to CRP level.

But serum obestatin and obestatin/ghrelin ratio was not significantly correlated with CRP level in this study.

In animal models of intestinal inflammation, leptin behaves as a pivotal mediator of inflammation(23). Also, chemically induced intestinal inflammation in rats resulted in elevated circulating leptin levels(24). But clinical researches about leptin level in patients with CD showed variable results(25, 26). In our study, serum leptin level was also correlated with CRP level ($p<0.001$), suggesting that serum leptin level can be an another potential surrogate marker of inflammation for CD patients. But there were no significant relationship between ESR and these adipocytokines.

In this study, we found that the serum ghrelin levels to be low in patients with history of abdominal surgery ($p=0.007$). Theoretically, patients who underwent abdominal surgery may have relatively decreased intestinal inflammatory burden after surgery. Furthermore, hypertrophied mesenteric fat tissue maybe decreased after surgery. Thus serum ghrelin may be decreased in patients with history of abdominal surgery. In previous studies, there was a negative correlation between ghrelin levels and BMI in general population(27). This result

suggests that ghrelin is not the cause of obesity or leanness, but is rather one aspect of the compensatory mechanisms that maintain body energy homeostasis(28). But in this study, the ghrelin level was not different according to BMI. In a previous study the hypertrophied mesenteric fat tissue in CD was independent of BMI or the presence of metabolic disorders, supporting this result(29).

Crohn's disease is a chronic, persistent and destructive disorder with different forms of clinical behavior(30). The disease may start as an inflammatory process with progressive development over time to complex disease with perianal involvement and fistula formation. The cumulative frequency of perianal fistula was reported to be 40.7% after 1 year, 46.1% after 5 years, 49.7% after 10 years, and 54.3% after 5 years in Korean CD patients(31). This differs from Western data, in which the cumulative frequency of perianal fistula was 13% to 38%(32). If a CD patient has a perianal involvement, it can be considered that the patient suffered long-standing inflammatory process. But exact etiology of perianal involvement including fistula in CD patient remains unclear. Distal colon disease, male gender, early age at diagnosis and

smoking are suggested risk factor for perianal disease although data are conflicting(33). Thus identifying factors such as serum markers related to perianal involvement are very important. Based on these disease nature, we performed analysis to evaluate the relationship between serum adiopcytokines and presence of perianal involvement. But we cannot find out a significant relationship between serum adipocytokine levels and presence of perianal involvement. Similarly, long term inflammatory process can result in clinically structuring or penetrating behavior. So the patients were categorized according to behaviors by Montreal classification (non-stricturing non-penetrating, stricturing, penetrating). But we cannot show significant deference of serum adiopcytokine levels among these behaviors.

Previous studies suggested that the clinical significance of serum CRP may depend on disease location(15, 34). Recent study demonstrated that CRP at diagnosis was associated with colonic or ileocolonic disease location than ileal disease(35). According to the Montreal classification, we divided patients by disease location into ileal, ileocolon and colon group. We performed analysis to compare serum adipocytokine levels with

disease location of CD. But there were no clear relationship between serum adipocytokine levels and disease location.

This study has several limitations. First, the patients were enrolled retrospectively: therefore, the measurement of adipocytokines was not performed at initial diagnosis. Second, direct data related to bowel inflammation such as CDAI was not calculated for all the included patients. So we cannot compare ghrelin level to intestinal inflammation or disease activity directly in all included patients. As a result, we analyzed data for inflammation via CRP indirectly, so we cannot find out the superiority of ghrelin and leptin level to CRP level for measuring intestinal inflammation. Third, histopathologic data were not available due to restrospective study design, so we cannot compare serum adiopocytokine level with the grade of mucosal inflammation directly.

In conclusion, our analysis showed that serum ghrelin and leptin levels can be surrogate inflammatory markers for CD, and in clinical practice may serve as useful tools to estimate disease activity, tailoring therapy, and to measure effect of treatment. Further investigations are required to determine accurate

correlation between disease activity and adipocytokine levels in CD patients.

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국문 초록

서론: 염증, 항염증, 염증 조절 인자 간의 균형이 크론병의 임상 경과를 결정짓는데 가장 중요한 요소이다. 염증 정도를 결정하는 것은 질환의 활성도를 평가하고 최적화된 치료를 하는데 필요하다. 크론병 환자에서 장벽에 국한되어 있던 염증 반응은 주위의 내장지방조직으로 침투할 수 있다. 활성화된 지방세포들은 렙틴, 아이포넥틴, 그렐린등의 매개 물질을 분비하게 된다. 본 연구는 크론병 환자에서 공복시 혈중 렙틴, 아디포넥틴, 오베스타틴, 그렐린을 측정하여 이러한 인자들이 크론병 환자의 장내 염증 정도와 질병 활성도를 대변할 수 있는 표지자가 될 수 있는지 알아보고자 한다.

방법: 2009 년 3 월 부터 2012 년 2 월 까지 국내 13 개 병원에서 크론병 환자의 혈액 샘플을 확보하고 임상지표를 분석하였다. 공복 혈중의 렙틴, 아디포넥틴, 오베스타틴, 그렐린 농도를 상용화된 ELISA 방법으로 측정하였다. 환자들의 특성을 몬트리올 분류에 따라 계층화 하고 의무 기록을 후향적으로 분석하였다. 이렇게 확보한 크론병 환자의 임상자료와 adipocytokine 농도의 관계를 분석하였다.

결과: 153 명의 크론병환자가 연구에 포함되었다. 단변량 분석에서 혈중 그렐린 농도는 환자의 나이 (p=0.041) 및 진단시의 나이 (p=0.017)와 음의 상관관계가 있었고 혈중 CRP 농도(p=0.017)와 통계학적으로 유의한 양의 상관관계가 있었다. 다변량 분석에서는 혈중 그렐린 농도와 CRP 만이 (p=0.032) 통계적으로 유의한 상관관계가 있었다. 혈중 렙틴 농도 역시 CRP 농도와 연관성이 있었다 (p<0.001). Adipocytokine 의 농도와 크론병의 위치 및 양상과는 유의한 상관관계가 없었다. 혈중 그렐린 농도는 이전에 복부 수술력이 있는 환자 군에서 없는 환자 군보다 유의하게 낮게 나타났다(p=0.007).

결론: 본 연구 결과 혈중 그렐린과 렙틴 농도는 크론병환자에서 염증 정도를 대변하는 잠재적인 지표가 될 수 있음을 밝혀냈지만 질병 활성도를 예측하는 임상적인 유용한 도구가 되기 위해서는 추가적인 연구가 필요하다.

주요어 : 그렐린, 렙틴, 크론병, 질병활성도, 염증
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