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Apelin Levels According to the Site of Involvement in Inflammatory Bowel Diseases

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ABSTRACT

Objective: Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), presents ongoing challenges in terms of diagnosis and management. With increasing treatment options, reliable markers for assessing treatment response have become crucial. This study explored the potential of apelin, a peptide hormone implicated in inflammation, as a biomarker for monitoring disease activity in patients with IBD undergoing colonoscopy.

Materials and Methods: The study included 91 patients who were followed up for IBD. Apelin levels were measured in serum, and the site of involvement was simultaneously examined by colonoscopy. Alternations of apelin levels depending on the location of involvement was also considered.

Results: Despite the widespread presence of apelin in the gastrointestinal system (GIS), our findings did not reveal significant differences in apelin levels among patients with varying colonoscopic involvement (p=0.73).

Conclusion: Although apelin has potential as a biomarker of gastrointestinal inflammation in IBD, its precise role and clinical applicability necessitate comprehensive studies involving larger patient populations. Future research on apelin and IBD could refine its utility in disease monitoring and enhance its diagnostic significance.

Keywords: Inflammatory bowel disease, apelin, Crohn's disease, ulcerative colitis

INTRODUCTION

Inflammatory bowel disease (IBD) has two chronic forms. Ulcerative colitis (UC) is a chronic inflammatory bowel disease characterized by remissions and exacerbations that involve the colonic mucosa without leaving intact tissue through various extensions from the rectum to the proximal. Crohn's disease (CD), in turn, affects the entire digestive tract from the mouth to the anus in a segmental and transmural manner, and it also presents with remissions and exacerbations; however, it should be known that both conditions are not specific to the digestive tract, but are systemic diseases with many extra intestinal symptoms. Factors such as genetic, environmental, and host immune responses are believed to be responsible for the etiology of these conditions. IBD has a complex diagnosis, which is based on clinical, endoscopic, and histological features (1, 2).

The treatment of both diseases is based on immunosuppressive therapy. In recent years, immunomodulatory therapies have been at the forefront. The increasing availability of new treatment options reduces morbidity among these patients. Alongside the expansion of treatment choices, numerous immunological

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markers used in monitoring have become crucial. The desirability of a noninvasive method for assessing treatment response is highly valuable (3).

In this context, biochemical markers have become increasingly popular in recent years. One pertinent marker is apelin, whose levels increase during inflammation and can be measured using a simple blood test. Apelin is a peptide hormone recently added to the adipokine family that is released from adipose tissue. It was first isolated from bovine gastric juice (4). Apelin and apelin receptor ligands have been identified in many tissues throughout the body. It is primarily present in the human body's gastric epithelium and myocardial tissue (5). Most studies on apelin focused on the cardiovascular system. This is because apelin is present in the entire endothelium, including arteries, veins, and small vessels. It has increased nitric oxide release and to have positive inotropic effects on the heart (6).

Apelin also plays an active role in the gastrointestinal system (GIS). Apelin receptors are commonly found in the GIS (gastric enterochromaffin, pancreatic, colonic epithelial cells, gastric fundus, duodenum, and ileum). It stimulates cholecystokinin secretion in the intestinal tract and increases gastric cell proliferation. In addition, it blocks histamine release from enterochromaffin cells of the stomach and causes less acid release from parietal cells (7, 8). It exerts an inhibitory effect on dose-dependent gastric emptying and intestinal transit.

Furthermore, examining the gastrointestinal effects of apelin led to the discovery of its effects on food intake. Centrally administered apelin decreased food intake, whereas intravenous apelin administration did not affect food intake. However, studies on this subject should be more consistent. This distinction has led to the thought that individual differences may be related to apelin (9).

The widespread presence of apelin in the GIS prompted us to consider whether its expression undergoes alterations during chronic inflammation. This study examined apelin levels in the peripheral blood of patients with IBD who exhibited segmental or total active disease during colonoscopy. We hypothesized that individuals with widespread colonoscopic disease might exhibit higher levels of apelin than those with borderline disease. Consequently, we assessed changes in the inflammatory involvement in this disease, which often requires frequent colonoscopy monitoring.

MATERIALS AND METHODS

The Code of Ethics of the World Medical Association (Declaration of Helsinki) was used for the experiments involving human subjects. All procedures were performed in compliance with relevant laws and institutional guidelines. The Non-Drug Clinical Research Ethics Committee of Haseki Training and Research Hospital obtained the study's ethical approval (date: 05.04.2017, IRB number: 476).

The study included patients diagnosed with IBD who were followed up at the Gastroenterology Clinic of Training and Research Hospital after obtaining written informed consent. Patients younger than 65 years who were diagnosed with IBD endoscopically and histopathologically were included in the

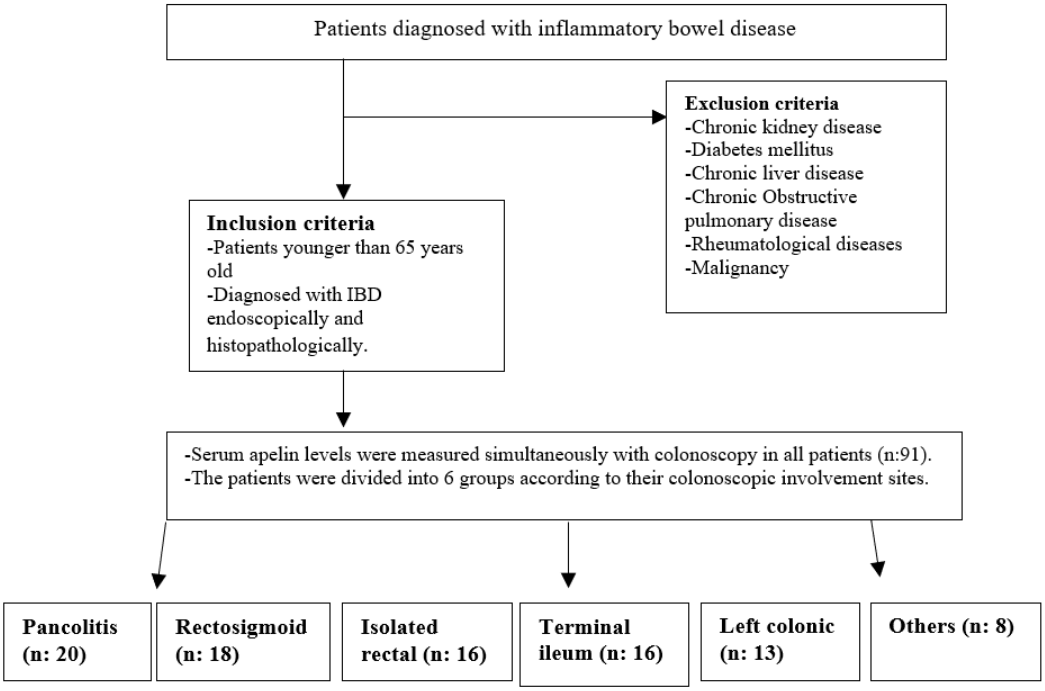

Figure 1. Patient flow chart. IBD, Inflammatory bowel disease.

study. Patients were divided into six groups according to their colonoscopic involvement sites (Figure 1).

The exclusion criteria were the presence of chronic kidney disease, diabetes mellitus, chronic liver disease, chronic obstructive pulmonary disease, rheumatologic diseases, and malignancies.

Biochemical Analysis

Samples were collected from venous blood and placed into gel tubes for apelin analysis. Within half an hour, the samples were centrifuged at 1000xg for 10 min and stored at -80°C. Serum apelin levels were detected using the Immulite 200 device (SIEMENS) with the CLIA (chemiluminescence immunoassay) method in all study patients. The site of involvement was demonstrated macroscopically and histopathologically by colonoscopy.

Statistical Analyses

The Statistical Package for the Social Sciences (SPSS) 15 statistical software (SPSS Inc, Chicago, IL, USA) for windows was used. Descriptive statistics were expressed as numbers and percentages for categorical variables, whereas the mean, standard deviation, and median were used for numerical variables. When the average distribution assumptions were unmet, a Kruskal-Wallis test was used to compare numerical variables between multiple groups. The alpha level of statistical significance was set as $p<0.05$.

RESULTS

The total number of patients with IBD was 91, consisting of 67 patients with UC and 24 patients with CD. The patients diagnosed with UC included 37 females and 30 males. Patients diagnosed with CD included 11 females and 13 males. The mean ages of patients with UC and CD were 38 and 31 years, respectively. The disease duration ranged from 4 to 22 years among patients with UC and from 1 to 13 years among patients with CD. The distribution of patients with inflammatory bowel disease by site of involvement was examined. Accordingly, 20 patients had pancolitis, 18 had recto-sigmoid arthritis, 16 had isolated rectal arthritis, 16 had terminal ileal arthritis, 13 had left colonic and 8 with others involvement (1 with transverse colonic, 2 with right colonic, 4 with caecal, and 1 with perianal).

Apelin's levels were analyzed by gender in IBD patients. The values were 1457.4 ± 1021.7 pg/mL in male patients and 1765.4 ± 1320.6 pg/mL in female patients. There were no significant differences in apelin levels between genders (p=0.323).

The apelin levels were compared with inflammatory markers routinely used during the follow-up of IBD. No significant association was found between C-reactive protein (CRP), sedimentation, hemoglobin, white blood cell (WBC), and apelin levels (Table 1).

Table 1. Comparison of apelin levels with other inflammatory markers and hemoglobin levels in patients with inflammatory bowel disease.

	Apelin Level (pg/mL)	
	rho	**p-value**
CRP	-0.132	0.231
Sedimentation	-0.085	0.440
Hemoglobin	0.036	0.745
Hematocrit	-0.012	0.917
WBC	-0.014	0.896

CRP, C-reactive protein; WBC, white blood cell.

Table 2. Comparison of apelin levels in inflammatory bowel disease according to site of involvement.

Site of Involvement	**n**	**Apelin level (pg/mL)**		
		Mean	**SD**	**Median**
Terminal Ileum	16	1522.6	1092.9	1154.0
Left Colon	13	1461.9	1238.7	841.7
Rectum	16	1645.5	1338.8	1012.0
Rectosigmoid	18	1661.8	1134.9	1231.2
Pancolitis	20	1843.1	1276.0	1560.0
Others	8	943.26	312.0	920.0

There were no significant differences in apelin levels between groups (p=0.730). n, number of samples; SD, Standard deviation.

This study compared the apelin levels of patients with IBD according to the site of involvement. Apelin levels did not differ significantly between patients divided into six group involvement sites on colonoscopy (p=0.730; Table 2).

DISCUSSION

Several inflammatory markers and biomarkers have been examined during follow-up of patients with IBD. Although some markers have contributed to assess the presence or absence of inflammation, most have been included in treatment follow-up. Especially fecal calprotectin, which has recently come into use, provides valuable information as a non-invasive inflammatory marker. In this regard, a study by Mosli et al. demonstrated that it was quite significant to examine fecal calprotectin in diagnosing patients with IBD (10, 11). Today, fecal calprotectin can also be used to identify new cases with suspected diagnosis. In addition, it can be examined regularly in patients diagnosed and followed up and provides beneficial results in remission activation (12). However, fecal calprotectin does not register elevated levels in diseases

characterized by ileal involvement. In other words, although it serves as a marker applicable to IBD with colonic involvement, the disease may be active in cases of ileal involvement. At the same time, fecal calprotectin levels remained within the normal range. Similar to apelin, fecal calprotectin cannot predict the extent of segmental involvement in colonic disease.

Apelin levels increase during inflammation and may elevate secondary responses arising from this inflammation. Lu et al. demonstrated a significant elevation in apelin levels in secondary cardiac hypertrophy induced by stress (13). Consistently, increased levels of angiotensin 2 were found in cardiac hypertrophy. This observation suggests the potential utility of apelin as a cardiac marker in the context of cardiac hypertrophy. Topuz et al. also demonstrated elevated apelin levels associated with cardiac stress, including cardiomyopathies (14).

The most compelling findings in cardiovascular studies are from data on patients with myocardial ischemia. Tycinska et al. observed elevated apelin levels in non-ST elevation myocardial infarction. Furthermore, the authors noted a significant association between high apelin levels and mortality within the first six months (15).

Apelin tends to increase even in chronic, slowly progressing inflammatory processes. Zarei et al. identified elevated levels of apelin and demonstrated that the levels of apelin released from adipose tissue are not influenced by dietary anti-oxidant levels (16).

Continuous inflammation followed by fibrosis during healing may contribute to elevated apelin levels. Kocer et al. observed elevated levels of apelin in renal interstitial fibrosis (17). Moreover, similar to our study, the authors demonstrated that this elevation was unrelated to CRP.

Experimental studies have shown a relationship between serum apelin levels and inflammatory bowel disease. These studies have shown that apelin levels are associated with trans mucosal inflammation of the colonic epithelium, stenosis, fibrosis, and mucosal healing. Song Han et al. (18) have also provided an essential guide for GIS. IBD-related studies include experimental investigations conducted by Song Han and colleagues. Experimentally inducing colitis and inflammatory bowel syndrome, the authors found elevated levels of apelin. In this study, experimental colitis was induced, and it was observed that exogenously administered apelin increased colonic proliferation (19-21). Additionally, it was noted that this marker released from the colonic epithelium could regulate epithelial proliferation. Consequently, the authors suggested that apelin plays a role in multiple stages of colonic differentiation. This proposition implies that apelin levels may vary among colon segments during inflammation.

A recent study by Mantaka et al. (22) compared the serum apelin levels in healthy individuals and patients diagnosed with IBD and found that the apelin level was significantly higher in patients diagnosed with IBD (p=0.012). The serum apelin level was found to be similar to that in our study. In this study, no distinction was made according to the location of involvement. However, no significant difference was found in the distinction according to the severity of endoscopic involvement (moderate-severe). The presence of a control group in the study by Mantaka et al. is an advantage of the study. The inclusion and exclusion criteria of patients, as well as the small sample size, are similar to those in our study. Mantaka et al. stated that the small number of patients was due to the COVID-19 pandemic (22).

In our study, we identified active sites of disease involvement using colonoscopy. During the same period, we investigated whether peripheral blood apelin levels differed according to the location of involvement. As anticipated, patients with active colonic involvement exhibited higher apelin levels. Although numerically higher in patients with pancolitis, no statistically significant elevation could be established, potentially due to our study's limited number of patients and samples. The lower incidence of pancolitis might be attributed to the presence of severe clinical symptoms and declining participation in the study. The most important limitation of this study is the small number of patients.

In conclusion, although apelin has been shown to be significant in various inflammatory conditions, its specific role in IBD remains complex and warrants further investigation. Prospective studies with a larger patient population focusing on apelin and IBD could provide more comprehensive insights into its potential as a biomarker for disease activity.

Ethics Committee Approval: Approval was received from the Non-Drug Clinical Research Ethics Committee of Haseki Training and Research Hospital (date: 05.04.2017, IRB number: 476).

Informed Consent: Informed written consent was obtained from the participants.

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Conflicts of Interests: The authors declare that they have no competing interests.

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