Research Article

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Efficiency and reliability of serum hepcidin level measurement in evaluation of disease activation in patients with ulcerative colitis

Ülseratif kolitli hastalarda serum hepsidin düzeyi ölçümünün hastalık aktivasyonunu değerlendirmedeki etkinliği ve güvenirliği

Efe Emre Kaşıkçı, Mustafa Çelik, Kadriye Akpınar

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Abstract

Purpose: The study is to examine the relationship between hepcidin and inflammation markers and disease severity.

Materials and methods: Hepcidin levels are determined in 108 Ulcerative Colitis patients and 56 control subjects, a total of 164 subjects, equally active and in remission. Correlations between hepcidin levels and Age, Gender, ESR, CRP, WBC Hb levels are determined in the data. The relationship between hepcidin level of active UC patients and Age, Gender, ESR, CRP, WBC, Hb, Truelove-Witts score and Mayo score is evaluated by regression analysis.

Results: ESR, CRP and Hepcidin levels in the Active Ulcerative Colitis group are statistically significantly higher than in the remission and control groups; ESR, CRP, Hepcidin levels are found to be statistically significantly higher in the entire ulcerative colitis group compared to the control group.

In addition, a statistically significant positive correlation is found between the hepcidin level and the Truelove Witts score and the Mayo score in the AUC group (p<0.05).In the regression analysis perform to determine the factors affecting hepcidin level in ulcerative colitis patients, increase in Age (B=0.143, p<0.05), increase in Truelove Witts Score (B=5.224, p<0.001) increased Hepcidin level, whereas increase in Erythrocyte Sedimentation Rate decreased hepcidin level (B=-0.160, p<0.05) is determined.

Conclusion: It is promising that serum hepcidin level can enter into clinical use as a marker that can be used to evaluate not only disease activation but also the severity of activation.

Keywords: Ulcerative colitis, hepcidin, inflammation markers.

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Öz

Amaç: Çalışmada hepsidin ile inflamasyon markerları ve hastalık şiddeti arasındaki ilişkinin irdelenmesi amaçlanmıştır.

Gereç ve yöntem: Bu çalışmada toplam 164 kişi katılmış olup eşit sayıda aktif ve remisyonda olmak üzere 108 Ülseratif Kolit hastası ile 56 kontrol kişisinin hepsidin düzeyleri belirlenmiştir. Elde edilen verilerde hepsidin düzeyleri ile yaş, cinsiyet, ESH, CRP, WBC Hb düzeyleri arasındaki korelasyonlar tespit edilmiş, aktif ÜK hastalarının hepsidin düzeyi ile yaş, cinsiyet, ESH, CRP, WBC, Hb, Truelove-Witts skoru ve Mayo skoru arasındaki ilişki regresyon analizi ile değerlendirilmiştir.

Bulgular: Aktif Ülseratif Kolit grubunda ESH, CRP ve Hepsidin düzeyleri remisyon ve kontrol grubuna göre istatistiksel olarak anlamlı düzeyde yüksek; tüm ülseratif kolit grubunda, ESH, CRP, Hepsidin düzeylerinin kontrol grubuna göre istatistiksel açıdan anlamlı düzeyde yüksek saptanmıştır. Ayrıca AÜK grubunda, hepsidin düzeyi ile Truelove Witts skoru ve mayo skoru arasında istatistiksel olarak anlamlı düzeyde pozitif yönde bir korelasyon bulunmuştur (p<0,05) ve ülseratif kolit hastalarında hepsidin düzeyini etki eden faktörleri saptamak için yapılan regresyon analizinde yaş artışının (B=0,143, p<0,05), Truelove Witts Skoru'nun artışının (B=5,224, p<0,001) hepsidin düzeyini arttırdığı; Eritrosit Sedimentasyon Hızının yükselmesinin ise hepsidin düzeyini azalttığı (B=-0,160, p<0,05) tespit edilmiştir.

Sonuç: Serum hepsidin düzeyinin yalnızca hastalık aktivasyonunu değil aynı zamanda aktivasyon şiddetinin de değerlendirilmesinde kullanılabilecek bir marker olarak klinik kullanıma girebileceği konusunda umut vadetmektedir.

Anahtar kelimeler: Ülseratif kolit, hepsidin, inflamasyon markerları.

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Efe Emre Kaşıkçı, Asst. Prof. Suat Seren Chest Diseases Hospital, Clinic of Allergy Immunology, İzmir, Türkiye, e-mail: drefemre@gmail.com (https://orcid.org/0000-0003-2156-836X) (Corresponding Author)

Mustafa Çelik, Assoc. Prof. Pamukkale University Faculty of Medicine, Internal Medicine/Gastroenterology Outpatient Clinic, Denizli, Türkiye, e-mail: mustafa.dr29@hotmail.com (https://orcid.org/0000-0001-8175-2324)

Kadriye Akpınar, M.D. Burdur State Hospital, Biochemistry Laboratory, Burdur, Türkiye, e-mail: dr.akpinar.kadriye@gmail.com (https://orcid.org/0000-0002-6951-8866)

Introduction

Ulcerative colitis (UC) is a chronic, recurrent disease whose inflammation is limited to the colonic mucosa, generally starting from the rectum and progressing proximally, progressing in attacks and remissions [1]. The symptoms of UC mainly include abdominal pain, diarrhea, mucus, pus and blood in the stool, and extraintestinal symptoms. In addition, UC may present with nonspecific symptoms such as fever, loss of appetite and weight, fatigue, and primary amenorrhea. The cause of the disease is seen as an abnormal immune response against intestinal flora [2]. Inflammatory bowel diseases such as UC and Crohn's Disease are characterized by the interaction of inflammatory and cytotoxic mechanisms. The Truelove-Witts classification and Mayo Scoring System are frequently used to evaluate disease activity, predict prognosis, and plan treatment in UC. In addition, clinical, laboratory, endoscopic, histopathological and radiological findings are used together in the evaluation process of patients with IBD. The most frequently used laboratory parameters in the evaluations are Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP), Cytokine levels, WBC (leukocyte), and Hemoglobin (Hb), Fecal biological markers (Calprotectin, S100, Lactoferrin).

Hepcidin molecule is a recently discovered low molecular weight hepatic peptide and plays an important role in iron metabolism. It is known that this molecule is affected by inflammation, iron stores, hypoxia, and anemia [3, 4]. Hepcidin is also a type 2 acute phase protein and is thought to be a primary regulator of iron homeostasis [5].

Studies have shown that hepcidin levels increase significantly in inflammatory disease [6]. Inflammation and infection increase hepcidin synthesis. Patients with sepsis, inflammatory bowel disease, myeloma, burns, and C reactive protein (CRP) levels >10 mg/dL exhibit significantly elevated hepcidin levels [7, 8]. The role of hepcidin in host defense and iron homeostasis also increases the interest in examining its relationship with UC disease. One study in patients with Ulcerative Colitis (UC), hepcidin levels were found to be reduced. This reduction was more pronounced in UC patients with anemia. It is suggested that utilizing hepcidin levels as a guide might be beneficial for the administration of oral iron supplements in patients with UC and other chronic inflammatory diseases [9].

In this study, it was aimed to evaluate the relationship between hepcidin and inflammation markers and disease severity. It was thought that the follow-up of hepcidin levels would be useful in the routine follow-up of UC patients, in predicting the severity of the disease, and in evaluating the response to treatment, supported by more comprehensive studies.

Material and method

This study was carried out in Pamukkale University Faculty of Medicine, Department of Gastroenterology between January 2018 and July 2019. A total of 108 patients who were active (54) and in remission (54) were followed up in the study, whose histopathology confirmed UC by colonoscopy and whose hepcidin levels complied with the exclusion criteria. In the control group, 56 healthy volunteers without any known disease in the anamnesis were included in the study. Patients (except for UC) and control group patients with any known systemic disease, findings suggestive of active infection, a history of malignancy, or a ferritin level above normal were not included in the study.

The Anamnesis, Age, Gender, Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP), leukocyte (WBC), hemoglobin (Hb), and levels of all participants were recorded and their averages were calculated (Table 1). Then, the relationship between Hepcidin level and Age, ESR, CRP, WBC, and Hb levels in all cases was evaluated by correlation analysis (Table 2). After this evaluation, a comparison was made between the 3 groups in terms of Age, Gender, ESR, CRP, WBC, Hb, and Hepcidin levels (Table 3). Age, Gender, ESR, CRP, WBC, Hb, and Hepcidin levels were compared between all UC patients (group 1 and group 2) and the control group (Table 4). In addition, the relationship between Hepcidin level and Age, ESR, CRP, WBC, and Hb levels in the whole UC group was evaluated by correlation analysis (Table 5). Finally, the Truelove-Witts score of all active UC patients was calculated and the shortened endoscopic Mayo Activation Score was determined by colonoscopy, the relationship between them was evaluated (Table 6) and a regression analysis was performed between the scores (Table 7).

Table 1. Age, Gender, ESR, CRP, WBC, Hb, and Hepcidin parameters levels in all cases

All Patients (n=164)	Average ± Standart Deviation
Age (Year)	41.54±14.54
Gender (Female)	82 (50%)
ESR (mm\dL)	23.68±15.39
CRP (mg\dL)	0.80±2.01
WBC (K\µL)	7.82±2.68
Hb (g\dL)	13.16±2.13
Hepcidin (ng/L)	10.06±6.08

Table 2. Correlation analysis between Age, ESR, CRP, WBC, and Hb levels in all cases

		Age (year)	ESH (mm\dL)	CRP (mg\dL)	WBC (K\µL)	Hb (g\dL)
Hepcidin (ng/L)	**R**	0.08	0.14	0.07	0.11	-0.12
	P	>0.05	>0.05	>0.05	>0.05	>0.05

Table 3. Comparison of Age, Gender, ESR, CRP, WBC, Hb, and Hepcidin levels of the three groups included in the study

	Group 1 (n:54)	Group 2 (n:54)	Group 3 (n:56)	*P* value
Age (year)	41.51±13.41	42.11±15.78	41.01±14.58	Gp1-Gp2 *p*>0.05 Gp1-Gp3 *p*>0.05
Gender (female)	27 (50%)	27 (50%)	28 (50%)	*p*>0.05
ESH (mm\dL)	33.70±17.71	21.40±12.12	16.33±9.74	Gp1-Gp2 *p*<0.001 Gp1-Gp3 *p*<0.001
CRP (mg\dL)	1.81±3.25	0.42±0.52	0.21±0.30	Gp1-Gp2 *p*<0.001 Gp1-Gp3 *p*<0.001
WBC (K\µL)	8.34±3.15	7.87±2.77	7.28±1.94	Gp1-Gp2 *p*>0.05 Gp1-Gp3 *p*>0.05
Hb (g\dL)	12.89±1.94	13.05±2.05	13.53±2.36	Gp1-Gp2 *p*>0.05 Gp1-Gp3 *p*>0.05
Hepcidin (ng/L)	13.37±6.69	8.08±5.41	8.80±4.38	Gp1-Gp2 *p*<0.001 Gp1-Gp3 *p*<0.01

Group 1: Active Ulcerative Group, Group 2: Ulcerative Group in Remission, Group 3: Healthy Control Group

Table 4. Comparison of all UC patients (group 1 and group 2) and control group in terms of Age, Gender, ESR, CRP, WBC, Hb, and Hepcidin levels

	UC patients (n:108)	Control Group (n:56)	*P* value
Age (Year)	41.81±14.58	41.02±14,59	>0.05
Gender (Female)	54 (50%)	28 (50%)	>0.05
ESR (mm\dL)	27.56±16.32	16.33±9.75	<0.001
CRP (mg\dL)	1.12±2.43	0.21±0.30	<0.001
WBC (K\µL)	8.11±2.97	7.29±1.95	>0.05
Hb (g\dL)	12.98±1.99	13.54±2.37	<0.05
Hepcidin (ng/L)	10.73±6.74	8.81±4.38	*<0.05*

Table 5. Correlation analysis of the relationship between Hepcidin level and Age, ESR, CRP, WBC, and Hb levels in all UC patients

		Age (year)	ESR (mm\dL)	CRP (mg\dL)	WBC (K\µL)	Hb (g\dL)
Hepcidin (ng/L)	**R**	0.035	0.098	0.044	0.129	-0.158
	P	0.718	0.312	0.653	0.183	0.103

Table 6. Correlation analysis of the relationship between Hepcidin level and Age, ESR, CRP, WBC, Hb, Truelove-Witts's score, and Mayo Score in active UC patient group

		Age (year)	ESR (mm\dL)	CRP (mg\dL)	WBC (K\µL)	Hb (g\dL)	Trulove-Witt Score	MAYO Score
Hepcidin (ng/L)	***P***	0.209	-0.146	-0.117	0.024	-0.085	0.293	0.286
	R	0.130	0.291	0.401	0.861	0,542	0.032	0.036

Table 7. Regression analysis between Hepcidin level and Age, ESR, CRP, WBC, Hb, Truelove-Witts Score, and Mayo Score in the active UC group

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Independent variables	**B**	**Std. Error**	***P***	**Min.**	**Max.**
Age (year)	0.143	0.060	0.021	0.022	0.264
ESR (mm\dL)	-0.160	0.053	0.004	-0.267	-0.053
Truelove-Witts Score	5.224	1.159	<0.001	2.894	7.554

The patient group, Age, ESR, CRP, WBC, Hb, Mayo and Truelove Scores were included in the model and backward linear regression analysis was performed. R2=0.31

Measurement of hepcidin level

For the measurement of hepcidin in serum, 9-10 mL of venous blood was drawn from all cases and sent to the laboratory rapidly. The serum of the blood, which was centrifuged 3' at 5000 rpm, was divided into Eppendorf tubes into 2-3 parts. The samples were stored in a deep freezer at -80ºC until the day of analysis and all samples were studied in one go.

In the study with Human BT ELISA kits, all samples and kits collected first were brought to room temperature. After the standards and chemicals of the kits were prepared, standards and samples were placed in the wells on the plate. Then, following the steps described in the package insert, the samples were colored according to their concentrations, and the absorbance values of the wells were read by using the Kayto RT -2100c Microplate reader at 450 nanometers (nm), and the results were printed out. Concentrations were calculated using the serum absorbance values found. Values found are pg/mL units for hepcidin.

Statistical analysis

The obtained data were transferred to the SPSS v25 (Chicago, Illinois, USA) Program and statistical analyzes were made. Differences between groups were evaluated using Mann Whitney U and Kruskal Wallis tests. Spearman correlation analysis was performed to examine the interaction of the variables with other parameters and the relationship between these parameters. Regression analysis was used to evaluate the relationship of these parameters between groups $p<0.05$ was accepted as significant for all tests.

Permission was obtained from Pamukkale University Non-Interventional Clinical Research Ethics Committee.

Results

Age, Gender, levels of ESR, CRP, WBC, Hb, and Hepcidin parameters common to all participants in the study are given in Table 1, and the results of correlation analysis between Age, and ESR, CRP, WBC, and Hb parameters are given in Table 2. As a result of the correlation analysis, no statistically significant correlation was found between Hepcidin level and Age, ESR, CRP, WBC, and Hb (p>0.05) (Table 2).

There was no statistically significant difference between the three groups in terms of age, gender, WBC, and Hb (p>0.05). When evaluated in terms of ESR levels, the ESR value of the AUC group was found to be statistically significantly higher than the RUC and control group (p<0.05). In CRP values, the results of the AUC group were found to be statistically significantly higher compared to the RUC and control group (p<0.001). Finally, when the hepcidin levels were compared, it was observed that the AUC group values were statistically significantly higher than the RUC and control groups (p<0.001) (Table 3).

There was no statistically significant difference between UC patients and control group- in terms of Age and Gender (p>0.05). When compared in terms of ESR and CRP levels, it was found that the values of the UC group were statistically significantly higher than the control group (p<0.001). In hepcidin and Hb levels, the values of the UC group were found to be statistically significantly higher than the control group (p<0.05) (Table 4).

In all UC patients (Remission and Active UC), no statistically significant relationship was found between Hepcidin level and Age, ESR, CRP, WBC, and Hb (p>0.05) (Table 5).

When the relationship between hepcidin level and age, ESR, CRP, WBC, Hb, Truelove-Witts score, and Mayo Score was evaluated with correlation analysis only in AUC patient group, no statistically significant correlation was found between Hepcidin level and Age, ESR, CRP, WBC, and Hb levels (p>0.05). A statistically significant positive correlation was found between Hepcidin level and Truelove -Witts score and Endoscopic Mayo Score (p<0.05) (Table 6).

In the regression analysis performed to determine the factors affecting Hepcidin levels in active UC patients, it was found that the increase in age and (B=0.143, p<0.05) Truelove Witts Score (B=5.224, p<0.001) increased Hepcidin level; it was determined that the increase in the Erythrocyte Sedimentation Rate decreased the Hepcidin level (B=-0.160, p<0.05) (Table 7).

Discussion

Many studies have evaluated whether there is a significant relationship between serum hepcidin levels and some laboratory parameters. In liver diseases, serum hepcidin levels are generally decreased, while hepcidin levels are increased in individuals with chronic renal failure [10, 11]. Various studies have also found an association between hepcidin and Crohn's disease and ulcerative colitis in patients with IBD and anemia [12].

There are numerous studies in the literature on the hepcidin molecule. The fact that the molecule was increased in inflammatory conditions in studies suggested that this molecule can be used as an alternative or adjunct to other inflammatory parameters in UC patients with endothelial-epithelial damage. Therefore, in our study, it was aimed to show whether hepcidin level in UC patients, its relationship with inflammatory markers, whether there is a correlation with various scoring systems developed to reflect UC disease activation, and if this correlation is provided, whether it can be used as a new alternative parameter to show disease activity. Since no statistically significant difference was found in terms of age and gender in the study, we can conclude that the groups were balanced and comparable among themselves.

Several studies have shown the relationship between hepcidin and inflammation in patients with IBD, and positive correlations were found between serum - urine hepcidin levels and CRP and IL-6 levels [13]. In this study, the ESR level was found to be significantly higher in the AUC group compared to RUC and control group (Table 3). In addition, the ESR level of the entire UC group was found to be significantly higher than the control group (Table 4). In the study of Semrin et al. [14] (2006) a positive correlation between CRP and hepcidin was found. In another study, no significant correlation was

found between hepcidin and disease activity and inflammation markers in inflammatory bowel disease [15]. In our study, when the AUC, RUC, and control group were compared in terms of hepcidin levels, hepcidin levels were found to be statistically significantly higher in the AUC group (Table 3). In addition, when we compared the whole UC group (AUC and RUC) and the SC group in terms of hepcidin levels, it was found that the hepcidin level was statistically significantly higher in the whole UC group compared to the SC group (Table 4). However, in the correlation analyses performed in the whole UC group and active UC group, no statistically significant correlation was found between ESR and CRP values and hepcidin levels. This result made us think that hepcidin levels increase with inflammation, as do CRP and ESR levels in UC patients, but this increase is independent of the increase in ESR and CRP. The idea that hepcidin level measurement shows inflammation independent of CRP and ESR levels and that it may be a more effective molecule showing activation in UC patients has been strengthened. With these findings, it is thought that the evaluation of activation by looking at ESR and CRP in AUC patients will be incomplete, and hepcidin level measurement may be useful in cases where activation cannot be evaluated with ESR and CRP.

Bleeding, leukocytosis and anemia secondary to chronic inflammation are the findings in active UC. In a study, it was reported that there were significant increases in hepcidin levels in individuals with IBD, and anemia was observed in 42% of them. As a result of multivariate analyzes, it was shown that serum hepcidin levels were correlated with ferritin and disease activity, but not with anemia. It was also found that hepcidin levels were lower in the patient group compared to healthy participants, independent of anemia status [16]. In another study conducted on healthy individuals and IBDs, serum hepcidin levels were found to be significantly lower in the IBD group. Decreased innate immunity, intestinal epithelial damage, and Paneth cell loss have been reported as the cause of this condition [17]. In our study, hepcidin levels in the AUC group and all UC groups were found to be statistically significantly higher than in the other groups, and no significant leukocytosis was found. The Hb level was found to be significantly lower in the entire UC group compared to the SC group (Table 4). This finding shows that AUC patients should not be evaluated based on WBC and Hb levels alone. Since no significant difference was observed between hepcidin and Hb in the correlation analysis, it can be concluded that hepcidin levels in UC patients are affected by inflammation rather than anemia. It was observed that there was a positive correlation between the scoring systems used in the study (Table 6). In the regression analysis performed in the AUC group, a significant correlation was found between the hepcidin level and the Truelove-Witts scoring system, which is one of the most important findings of this study (Table 7).

ESR, CRP, WBC, Hb, etc. Parameters used to evaluate disease activation, such as the disease, only find a place for themselves in scoring systems. From this point of view, according to the result of our study, hepcidin was found to be superior to other parameters in reflecting disease activation alone, which other laboratory parameters could not. The fact that ESR and CRP levels were insufficient in the AUC group and did not show any statistically significant difference in scoring systems, while hepcidin was higher compared to the other groups indicates that it may be a serum marker. The reason for the variability of hepcidin levels between studies may be due to the complex pathophysiological mechanisms involved in hepcidin regulation. Because hepcidin level varies depending on many factors such as iron storage in the body, hypoxia, and inflammation.

These results suggest that serum hepcidin level may enter into clinical use as a marker that can be used to evaluate not only disease activation but also the severity of activation. Controlled studies in which hepcidin levels can be shown to decrease with treatment in active UC patients may provide useful information on whether hepcidin measurement can be used as a useful marker in the follow-up of treatment response. In this study, it was aimed to evaluate the relationship between hepcidin and inflammation markers and disease severity. It is thought that the follow-up of hepcidin levels may be useful in the routine follow-up of the patients, in the prediction of the severity of the disease, and in the evaluation of the response to the treatment, supported by more comprehensive studies.

Conflict of interest: No conflict of interest was declared by the authors.

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Authors' contributions to the article

M.C. and E.E.K. constructed the main idea and hypothesis of the study and developed the theory and arranged/edited the material and method section. E.E.K. and K.A. has done the evaluation of the data in the results section. The discussion section of the article was written by M.C. and E.E.K. who also reviewed, corrected, approved it. In addition, all authors discussed the entire study and approved the final version.