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Ulcerative Colitis and Neopterin: Related?

Ülseratif kolit ve Neopterin: İlişkili mi?

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ABSTRACT

Objectives: Ulcerative colitis (UC) is a chronic inflammatory bowel disease that invades the colon mucosa and progresses with remissions and exacerbations. Neopterin is a biochemical marker of cell-mediated immunity. Studies have demonstrated increased levels of neopterin in inflammatory bowel diseases. The aim of this study was to examine the relationship between the Truelove-Witts criteria and the level of neopterin in UC patients, as well as the usefulness of neopterin in determining the activity of the disease.

Methods: Thirty-three patients who were followed-up for UC in the gastroenterology clinic of a single hospital were enrolled in the study and divided into 3 groups: mild, moderate, and severe UC, according to the Truelove-Witts activity index. A control group of 43 healthy individuals was also included in the study. The neopterin level of the patient and the control groups was examined and the relationship was statistically analyzed.

Results: No statistically significant difference was detected in the median neopterin level between the patient and the control groups.

Conclusion: These results demonstrated that the serum neopterin level remained unchanged in patients with UC when compared with the control group, and that age and gender did not have any specific impact on this outcome.

Keywords: Inflammatory bowel disease; neopterin; ulcerative colitis.

ÖZET

Amaç: Ülseratif kolit (ÜK), kolon mukozasını istila eden, remisyon ve alevlenme ile ilerleyen kronik bir enflamatuvar barsak hastalığıdır. Neopterin, hücre aracılı immünitenin biyokimyasal bir belirtecidir. Çalışmalar, İnflamatuar barsak hastalıklarında neopterin düzeylerinde artış olduğunu göstermiştir. Bu çalışma, Ülseratif kolitte Truelove-Witts aktivite kriterleri ile neopterin düzeyi arasıdaki ilişkiyi ortaya koymayı ve Neopterinin hastalık aktivitesini göstermede kullanılabilirliğini göstermeyi amaçlamaktadır.

Yöntem: Hastanemiz Gastroenteroloji kliniğinde ÜK nedeniyle takip edilen 34 hasta çalışmaya alınıp, hastalık aktiviteleri açısından Truelove-Witts akvitive indeksine göre hafif, orta ve şiddetli olmak üzere üç sınıfa ayrıldı. 43 adet sağlıklı birey, kontrol gurubu olarak çalışmaya dahil edildi. Hasta ve kontrol grubunda Neopterin düzeyi incelenip, aralarındaki ilişki istatistiksel olarak incelendi.

Bulgular: Hasta ve kontrol grubu arasında medyan neopterin düzeylerinde istatistiksel olarak anlamlı bir fark bulunmadı.

Sonuç: Bu sonuçlar serum neopterin düzeylerinin ülseratif kolitli hastalarda kontrol grubuna göre değişmediğini ve yaş ve cinsiyetin bu sonuç üzerinde belirli bir etkisi olmadığını göstermiştir.

Anahtar sözcükler: İnflamatuvar barsak hastalıkları; neopterin; ülseratif kolit.

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Ulcerative colitis (UC) is a chronic inflammatory bowel disease, which invades the colon mucosa in different lengths from the rectum to the proximal but without leaving any healthy segment inbetween and progresses with remissions and exacerbations.[1] Although the

etiology of ulcerative colitis is not exactly known, findings show that it is caused by a chronic immunological response to antigenic stimulation.[2] Inflammatory bowel diseases involve both excess in mucosal inflammation processes and defects in mechanisms suppressing this inflammation.[3]

In fact, ulcerative colitis is not only a digestive tract disease, but also a systemic disease with many kinds of non-intestinal retention.[4] Its clinical signs arefrequently rectal bleeding, diarrhea and abdominal pain. Medical treatment is effective in controlling the disease activity. Surgical treatment (total colectomy) is curative.[5]

Identifying whether the disease is active or not, is essential for the planning of treatment and determination of the prognosis.[1] Truelove-Witts have developed a system to classify patients with UC as mild, moderate and severe disease through their symptoms, physical examination findings and laboratory values. This classification will help the clinician decide on the treatment plan.[6,7]

Neopterin is a biochemical marker of cell-mediated immunity. It is generated by the activity of monocytes/macrophages and released into body fluids.[8] The level of neopterin is an indicator of the oxidative stress induced by the immunological system.[5] Studies have shown increased levels of neopterin in Inflammatory Bowel Diseases.[9]

Neopterin is excreted in an unchanged form via the kidneys.[8] An abnormal level of neopterin may be observed in various clinical cases; including infections, allograft rejection, autoimmune diseases, malignancies, heart failure, renal impairment and myocardial infarction.[10] A strong connection has been shown between neopterin levels and the severity and progression of infectious and inflammatory diseases.[11]

This study aims to show the relationship between the Truelove-Witts activity criteria and the level of neopterin in ulcerative colitis and the usability of neopterin in determining the activity of the disease.

Methods

Before starting the study, approval was obtained from the local Ethics Committee (16 march 2012, Decision number: 92), a Power Analysis was performed, and the size of the sample expected to be clinically significant (power of 80%) was identified. Patients who had been followed up for ulcerative colitis in the Gastroenterology Clinic at our hospital were invited for an examination between March and June 2012 and included into the patient group. Patients who did not have any autoimmune disease, infectious disease or malignant tumoral disease, and therefore with no history of using medication, and who were evaluated as having normal colonoscopy results; were included into the study as the "control group".

34 people in the patient group were classified for their ulcerative colitis activity as mild (n=13), moderate (n=18), and severe (n=3) based on the Truelove-Witts activity index and included into the study after their consents were obtained.

Venous blood samples were collected from the study and control groups to examine the level of neopterin all at once.

Statistical analysis

Statistical analyses were performed with SPSS 11.5 package software. The compliance of continuous variables to the normal distribution was investigated using the Kolmogorov-Smirnov test. Variables displaying Gaussian distribution were shown as average±SD, while variables displaying non-Gaussian distribution were shown as median (25^{th} to 75^{th} percentiles). The Mann-Whitney U test was used in the group comparisons of variables with abnormal distribution. The correlation between the variables was assessed with the Spearman correlation coefficient (rs). The Yates continuity correction test was used in the comparison of observed and expected values.

Potential confounders, which may coexist with the factor examined and may have a specific impact on the result, were counteracted with the two-way ANOVA and covariance analyses. In this analysis, a reciprocal transformation was performed for the variables displaying non-Gaussian distribution. Statistical significance was considered at $p<0.05$ (two-tailed).

Results

Demographics, clinical findings, laboratory values, and neopterin levels of the patient and control groups are shown in Table 1 and Table 2. While the difference in female/male ratios was not statistically significant between the two groups, average age was significantly lower in the patient group.

No statistically significant difference was detected in the median neopterin levels between the patient and control groups (Table 2).

Table 1. Demographics and clinical findings in the patient (n=34) and control (n=43) groups

	Patient group (n=34)	Control group (n=43)	p
Gender, male/female	22/12	19/24	0.118
Age (years)	43±13	52±16	0.012
Duration of disease (years)	1.00 (0.11–2.25)	-	-
Clinical activity, n (%)			
Mild	12 (35.3)		
Moderate	18 (52.9)	-	-
Severe	3 (8.8)		
Retention site, n (%)			
Proctitis	4 (11.8)		
Distal colon	14 (41.2)		
Left colon	11(32.4)	-	-
Generalized	3 (8.8)		
Pancolonic	2 (5.9)		
Drug use, n (%)			
Non-users	13 (38.2)		
Mesalazine	20 (58.8)	-	-
Mesalazine+Methylprednisolone	1 (2.9)		

Table 2.Laboratory data and Neopterin levels in the patient and control groups

	Patient group (n=34)	Control group (n=43)	p
WBC, x103/µL	9.5±2.4		
Hemoglobin, g/dl	12.6±1.9		
HCT, %	37.6±5.0		
PLT, x103/µL	332±104		
Sedimentation, mm/h	26±19		
CRP, mg/dl	1.04 (0.40–2.22)		
Neopterin, nmol/L	1.79 (1.49-2.20)	1.71 (1.46-2.26)	0.984

Possible effects of variables (age, gender) which might have a potential confounder effect on the neopterin levels were assessed. Analysis revealed no significant difference in the age-adjusted average of reciprocal transformed neopterin levels between the patient and control groups (F=0.328; p=0.569).

These results demonstrated that serum neopterin levels remained unchanged in patients with ulcerative colitis compared to the control group, and age and gender did not have any specific impact on this outcome.

As a result of this study, the comparison among groups with mild, moderate and severe clinical activity, as well as drug-using and non-drug-using subgroups, did not show any statistically significant difference in neopterin levels.

Discussion

There are 2 variables determining the treatment approach in ulcerative colitis. These are the severity and the retention site of the disease. In this study, to determine the clinical activity of patients we used the Truelove-Witts activity scoring, which is also frequently used by gastroenterologists in clinical practice.

Neopterin is a pteridine compound of low molecular weight. In active monocytes/macrophages, it is synthesized from GTP via the GTP cyclohydroxylase enzyme. In these cells, the final product of the pteridine metabolism is neopterin. [13] The fact that high neopterin levels reflect cellular immune activation was demonstrated in vivo on humans and primates, and in vitro in many monocyte culture studies

while it was argued that neopterin could be used as an activation marker for various diseases.[1]

As a result of the activation of the immune system by various antigenic stimulations, T-lymphocytes and NK cells are activated and secrete INF-γ. In humans, INF-γ has been argued to be the most potent inducer of neopterin.[13]

Measurement of neopterin levels in body fluids, especially for autoimmune diseases, reflects the local macrophage activity in this area. Secretion of neopterin by active monocytes/macrophages starts three days prior to the maximization of the T-lymphocyte proliferation and reaches its peak value approximately 1 week prior to the positivation of specific antibodies.[1] Therefore, although neopterin is considered usable as an early inflammation indicator, serum neopterin levels are reported to be higher than healthy controls in cases such as chronic disease in which the cellular immunity is continuously active.[14]

Studies were conducted in various autoimmune, infectious, and malignant diseases, considering that neopterin levels in serum body fluids can be used to assess cellular immunity. Serum neopterin levels are reported to increase in such diseases and to be a clinical and prognostic indicator of the existing disease.[15]

In a study conducted by Ertuğrul et al.[16] to show the relationship between inflammatory bowel diseases and serum neopterin levels, a relationship with clinical significance was demonstrated between neopterin levels in active andremission UC patients (p=0.041). The same study also found a statistically significant relationship between two clinical conditions, bloody stool and high fever, and the serum neopterin levels, as well as endoscopic activity index and the serum neopterin levels in UC patients. The study by Ertuğrul et al.[16] demonstrates that serum neopterin levels can be used as a parameter showing the disease activity in UC patients.

To identify the activation of inflammatory bowel diseases, Niederwieser et al.[17] looked at the urine neopterin levels in 25 UC patients. For UC, it was emphasized that neopterin excretion could be used in clinical observation as a parameter showing the activation.

In support of this study, a significant relationship was detected between the serum neopterin levels and disease activity by Tilg et al.[18] in 52 IBD patients and by Forrest et al.[20] in 12 IBD patients.

In the literature, there are studies which give results contrary to those mentioned thus far. In a study by Propst et al.,[19] serum neopterin levels were observed in 80 IBD patients and determined to be unrelated to the disease activity in UC.

In another study by Forrest et al. on the relationship between UC and neopterin levels, no significant difference was found among neopterin levels in patients going from active disease into remission.[20]

Just as in these two studies, this present study also detected no statistically significant difference in median neopterin levels between the patient and control groups.

If we take other studies in the literature into consideration along with this present study; although neopterin is a molecule that has been studied for around 25 years, clinical studies with a higher number of patients which make comparisons with other biochemical parameters are needed to determine its relationship with inflammatory bowel disease and its area of use in clinical practice.

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Disclosures

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