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Natural coagulation inhibitory proteins and activated protein C resistance in Turkish patients with inflammatory bowel disease

Türk inflamatuvar barsak hastalarında doğal koagülasyon inhibitör proteinleri ve active protein C direnci

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Background/aims: *Thromboembolic events are a rare but significant complication of inflammatory bowel disease. The aim of this study was to investigate the level of natural coagulation inhibitors and activated protein C resistance in Turkish patients with inflammatory bowel disease.* ***Methods:*** *Fifty patients (29 male, 21 female) without venous thrombosis history and 37 healthy controls were included in the study. Erythrocyte sedimentation rate, C-reactive protein, thrombocyte count, prothrombin time, activated partial thromboplastin time, fibrinogen concentration, von Willebrand factor antigen, factor VIII activity, activated protein C resistance, functional levels of antithrombin III, protein C and protein S were measured. Patients and controls with activated protein C resistance were further studied using a polymerase chain reaction assay for factor V Leiden mutation.* ***Results:*** *There was no significant difference between patients and the controls in terms of antithrombin III, protein C, protein S, factor (F) VIII and Willebrand factor levels. The mean thrombocyte counts, fibrinogen levels, and Willebrand factor levels were found to be significantly higher in patients who were in the active period of the disease than in controls and patients in remission. No significant difference was observed in those showing activated protein C resistance and factor V Leiden mutation between patients and controls.* ***Conclusions:*** *The presence of inherited thrombophilic defects, in particular activated protein C resistance and natural coagulation inhibitor deficiency, is uncommon in Turkish patients with inflammatory bowel disease in both active and remission periods. As a result, a controlled study in inflammatory bowel disease patients with thrombosis history is recommended.*

Key words: Natural coagulation inhibitor protein, activated protein C resistance, thromboembolism, inflammatory bowel disease

Amaç: *Tromboembolik olaylar inflamatuvar barsak hastalıklarının nadir fakat anlamlı bir komplikasyonudur. Bu çalışmada amaç inflamatuvar barsak hastası olan Türk hastalardaki doğal koagülasyon inhibitörlerinin seviyesinin ve aktive protein C direncinin araştırılmasıdır.* ***Yöntem:*** *Tromboz öyküsü olmayan 50 hasta (29 erkek, 21 kadın) ve 37 sağlıklı kontrol çalışmaya alındı. Eritrosit sedimentasyon hızı, C reaktif protein, trombosit sayısı, protrombin zamanı, aktive parsiyel protrombin zamanı, fibrinojen, von Willebrand faktör antijeni, FVIII aktivitesi, aktive protein C rezistansı, Antitrombin III, protein C and protein S fonksiyonel düzeyleri ölçüldü. Aktive protein C rezistansı olan hasta ve kontrollerde daha sonra polimeraz zincir reaksiyonu kullanılarak faktör V Leiden mutasyonu çalışıldı.* ***Bulgular:*** *Hasta ve kontroller arasında Antitrombin III, protein C, protein S, FVIII ve von Willebrand faktör düzeyleri arasında anlamlı fark yoktu. Remisyondaki hastalar ve kontrollerle kıyaslandığında ortalama trombosit sayısı, fibrinojen düzeyi, von Willebrand faktör düzeyi hastalığın aktif döneminde anlamlı olarak yüksek bulundu. Aktive protein C rezistansı ve faktör V Leiden mutasyonu gösteren hasta yüzdesinde hasta ve kontroller arasında anlamlı bir fark gözlenmedi.* ***Sonuç:*** *Tromboza eğilim gösteren aktive protein C rezistansı ve doğal koagülasyon inhibitörlerin eksikliği gibi kalıtsal bozuklukları aktif dönemdeki ve remisyondaki inflamatuvar barsak hastası olan Türk hastalarda saptamadık. Tromboz öyküsü bulunan hastalarda böyle bir kontrollü çalışma yapılmasını öneririz.*

Anahtar kelimeler: Doğal koagülasyon inhibitör proteinleri, aktive protein C direnci, tromboemboli, inflamatuvar barsak hastalığı

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INTRODUCTION

Thromboembolism is a well-described complication of inflammatory bowel disease (IBD), with a reported incidence of 1-6% (1-2). Although clinically significant thrombosis occurs in only a fraction of patients with IBD, it contributes significantly to patient morbidity and mortality. Autopsy studies report a much higher incidence of thrombosis, ranging from 7-39%, which is often responsible for patient mortality (3). Although thrombosis may be venous or arterial, the majority occur in veins (4). The most common thrombotic manifestations in IBD are deep vein thrombosis of the leg and pulmonary emboli (5). Crohn's disease (CD) characterized by a granulomatous vasculitis and intravascular fibrin deposition is a feature of this condition (6). Capillary microthrombi in otherwise normal tissue from patients with CD have also been reported, suggesting that vascular damage occurs at an early stage in the disease process. There is also histological evidence that small vessel occlusion may be important in the pathogenesis of ulcerative colitis (UC) (7, 8). It is recognized that a hypercoagulable state exists in IBD that involves all components of the clotting system. This hypercoagulable state has been suggested to be linked to the disease pathogenesis. Especially in CD, it has been demonstrated that microvascular thromboses occur in association with granulomatous or lymphocytic inflammation of the affected blood vessels (9). The thrombotic risk in IBD has been attributed to the hypercoagulable state and appears to increase with disease activity (2-3). But endothelial injury and increased thrombin generation with the presence of increase in plasma markers of activated coagulation have been documented in patients with both active and quiescent IBD (2-4, 6, 10). The protein C pathway is one of several natural anticoagulant systems. Protein C is a vitamin K-dependent protein, and its activated form (activated protein C, APC) controls the coagulation process by cleaving and inactivating factor VIIIa (FVIIIa) and FVa in the presence of protein S (11, 12). In 1993, Dahlback et al. (12) reported a link between poor anticoagulant response to APC and familial thrombophilia. In APC resistance (APCR), the patient's plasma does not exhibit the normal anticoagulant response to addition of APC, as reflected in a prolongation of the activated prothrombin time (APTT). It was later shown that this phenomenon of APCR was due to the replacement of arginine 506 with glutamine in the factor V molecule (FVR506Q, factor V Leiden), which was resistant to degradation by APC (5, 13-15). Resistance of factor V to degradation by APC (activated protein C resistance) is a major cause for venous thrombosis and is found in approximately 30% of patients with thromboembolisms and in 3% of healthy individuals (1, 16-18). The abnormalities which are seen in the active period of IBD are thrombocytosis, hyperfibrinogenemia, increased levels of FV and FVIII, and decreased levels of some coagulation inhibitors as antithrombin III (ATIII), protein C, and protein S (3, 14, 18-21). In the active and inactive period of the disease, fibrinopeptide A, and F1 and F2 prothrombin fragments increase (14, 21). The level of FVIIIa decreases in the active phase of CD. Other fibrinolytic abnormalities such as high plasminogen activator inhibitor and increased D-dimer levels play a central role in IBD pathogenesis by increasing the results of the initial vascular lesion. The importance of antiphospholipid, anticardiolipin antibodies and lupus anticoagulants is debatable (19-22).

In this study, the IBD patient group and healthy control group were compared according to coagulation abnormalities.

MATERIALS AND METHODS

Patients and Controls

We included 50 patients (29 male, 21 female) who were treated in Atatürk Research and Training Hospital, Gastroenterology Clinic and outpatient clinic, between 1999 and 2002, all of whom had been diagnosed as IBD. None of the patients had history of venous thrombosis. Eight patients were diagnosed as CD while the other 42 were diagnosed as UC. The median age of patients was 35.5 years (range 17-69 years). The median age of controls (22 male, 15 female) was 35 years (range 21-51 years). The difference in age and sex was not statistically significant between the patients and controls ($p=0.4$ and $p=0.9$, respectively). CD and UC were diagnosed by conventional clinical, radiological, endoscopic and histological criteria. In the beginning of the study, the Clinical Activity Index (CAI) and endoscopic score for the UC patients were determined according to Seo and Rachmilewich, while Crohn's Disease Activity Index (CDAI) and Harvey–Bradshaw Index were used for CD patients (23, 24). In 34 patients with UC (81%), CAI was higher than 150 (>150), and in 38 patients (90%) Rachmilewich endoscopic score was higher than 4 (>4). CDAI was higher than 150 (>150) and

Table 1. Clinical data related to 50 patients with IBD and 37 healthy controls [median value (minimum and maximum values)

	Ulcerative Colitis	Crohn's Disease	Control
Number	42	8	37
Sex (F/M)	24/18	5/3	22/15
Age	36 (17- 69)	31 (17-40)	35 (21-51)
CAI/CDAI	173 (86.60-265.8)	155.5 (14-414)	
EAI	7 (3-12)		
Therapy			
5-ASA	42	8	
Prednisolone	-	-	
Azathioprine	-	-	

CAI: Clinical activity index, CDAI: Crohn's disease activity index, EAI: Rachmilewich's endoscopic activity index

Harvey-Bradshaw Index was higher than 4 (> 4) in six patients with CD (75%). The clinical data about the patients are shown in Table 1.

Laboratory Studies

The venous blood samples from patients and controls were taken into plastic tubes containing 3.8% trisodium citrate (4.5 ml blood sample and 0.5 ml citrate). After centrifugation by 3000xg for 20 minutes, prothrombin time (PT), APTT and fibrinogen were measured, and the plasma samples were kept at -70°C until time of analysis. All laboratory examinations were performed by Thrombolyser Compact XR (Organon Technica) Coagulation Analyzer. PT, APTT and fibrinogen were measured by standard methods (Simplastin Excel, Platelin LS, Fibroquick, Organon Technica, Durham, North Carolina, USA). The functional level of ATI-II and protein C in the plasma were measured by routine chromogenic method as it takes the amidolytic method as a base in which synthetic chromogenic substrate is used (Chromostrate Antithrombin 3 Assay, MDA Protein C, Organon Technica, North Carolina, USA). The activity of plasma protein S was measured by a coagulation method similar to standard factor measurement (Bioclot Protein S-300 ACT, Biopool International, Ventura, CA, USA). The measurement of plasma factor VIII (FVIII) activity was made by the standard method in which the APTT test was made using the differently diluted plasma samples and FVIII deficient plasma samples (FVIII Deficient Plasma, Organon Technica, Durham, North Carolina, USA). APCR was measured by APTT tests performed with or without APC (Coatest APC Resistance 5, Chromogenix, Milano, Italy). Normal APC rate was higher than 1.8 (>1.8), and APC rate lower than 1.8 (<1.8) was accepted as APCR. Patients and controls with APCR were further studied using a polymerase chain reaction (PCR) assay for factor V Leiden mutation. The analysis of factor V Leiden mutation was performed on EDTA-anticoagulated blood according to the procedure described by Bertina et al. with small modifications (20). Immunoturbidimetric method was used for the quantitative measurement of von Willebrand factor (vWF) antigen (STA-Liatest VWF, Diagnostica Stago, Asni_res, France). The C-reactive protein (CRP) level was measured by Delta nephelometer (Seac s.r.l., Radim Group, Roma, Italy).

Statistical Analysis

The results are given as frequency, ratio, median, mean value ± standard deviation and range. For the correlation of the patients and controls according to sex and APCR ratio, chi-square test and Fisher's exact test, and for the other statistics Mann-Whitney U test were used. $p<0.05$ was accepted as statistically significant.

RESULTS

Coagulation data are summarized in Tables 2-4. There was no significant difference between the

Table 2. Coagulation parameters in patients with IBD and controls [Mean value±standard deviation, frequency (%)]

	Patients/Controls (number)	Patients (IBD)	Controls	p value (<0.05)
Thrombocyte (x10^9/L)	47/37	384.6±479.8	251.7±65.5	0.005*
PT (seconds)	50/36	12.6±1.8	11.9±1.8	0.08
aPTT (seconds)	50/37	29.4±4.0	31.1±4.7	0.29
Fibrinogen (mg/dl)	50/37	293.2±79.8	245.1±80.7	0.001*
Factor VIII (%)	46/32	167.3±122.4	165.3±98.5	0.84
vWF (%)	47/31	69.8±30.5	59.9±19.1	0.11
ATIII (%)	47/32	110.7±36.8	100.4±51.9	0.06
Protein C (%)	45/34	100.9±39.5	105.9±35.9	0.61
Protein S (%)	25/9	160.8±116.8	121.8±74.5	0.45
APCR [number (%)]	50/37	3 (6%)	1 (2.7%)	0.63
Factor V Leiden mutation [number (%)]	50/37	1 (2%)	0	1.00

PT: Prothrombin time, APTT: Activated partial thromboplastin time, vWF: von Willebrand factor, ATIII: Antithrombin III, APCR: Activated protein C resistance, *: p value with statistical significance

Table 3. Coagulation parameters in the patients with IBD in active period and controls [Mean value±standard deviation, frequency (%)]

	Patients in active period/controls (number)	Patients in active period (IBD)	Controls	p value (<0.05)
Thrombocyte (x10^9/L)	39/37	415.8±521.5	251.7±65.4	0.00*
PT (seconds)	41/36	12.7±1.9	11.9±1.8	0.07
APTT (seconds)	41/37	28.9±3.9	31.19±4.7	0.11
Fibrinogen (mg/dl)	41/37	300.9±85.2	245.1±80.7	0.001*
Factor VIII (%)	37/32	163.0±109.0	165.3±98.5	0.90
vWF (%)	40/31	73.5±30.7	59.9±19.1	0.036*
ATIII (%)	39/32	111.9±37.3	100.4±52	0.06
Protein C (%)	38/34	100.6±42.3	105.7±35.9	0.58
Protein S (%)	21/9	180.4±117.5	121.8±74.5	0.18

PT: Prothrombin time, APTT: Activated partial thromboplastin time, vWF: von Willebrand factor, ATIII: Antithrombin III, *: p value with statistically significance

patients and controls regarding means of PT and APTT. The mean thrombocyte counts and fibrinogen levels were significantly higher in patients with IBD (p<0.005 and p<0.001, respectively). There was no significant difference between patients and controls in terms of ATIII and protein C and protein S levels. There was no significant difference between the patients and controls in plasma FVIII and vWF levels. The mean thrombocyte counts, fibrinogen levels, and vWF levels were found to be significantly higher in patients who were in active period of the disease when compared with controls (Table 3) (p=0.00, p=0.00 and p=0.03, respectively). The mean platelet counts, vWF levels, and protein S levels were found to be significantly higher in patients who were in active period when compared with those in remission (p=0.01, p=0.02, p=0.02, respectively). Three of 50 patients (6%) with IBD and 1 of 37 healthy controls (2.7%) had APC resistance by plasma testing for APCR. No significant difference was observed for mean APC ratio and the percentage of patients showing APCR between IBD patients and controls (p=0.63). Samples from 3 patients and 1 control with APCR lower than 1.8 were analyzed for the factor V Leiden mutation with a PCR-based method and one patient with UC was found to be heterozygous for factor V Leiden. The mutation was not detected in any of the controls with low APC ratio. There was no significant difference in factor V Leiden mutation frequency between patients and controls (p=1.00). There was no significant difference between the compared groups in terms of other parameters.

DISCUSSION

Thromboembolic events are serious complications in patients with IBD (1, 5). The role of well-known hereditary thrombophilic conditions (plasma ATI-II, protein C and protein S deficiency and APCR)

Table 4. Coagulation parameters, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in the patients with IBD in active period and remission [mean value±standard deviation, frequency (%)]

	Patient number in active period/ Patient number in remission	Patients in active period	Patients in remission	P value (<0.05)
Thrombocyte (x10^9/L)	39/8	415.8±521.5	232.6±66.8	0.015*
PT (seconds)	41/9	12.7±1.9	12.4±1.9	0.72
APTT (seconds)	41/9	28.9±3.9	31.9±3.2	0.06
Fibrinogen (mg/dl)	41/9	300.9±85.2	258.3±31.7	0.13
Factor VIII (%)	37/9	163±109	185.2±174.4	0.74
vWF (%)	40/7	73.5±30.7	48.7±20.2	0.026*
ATIII (%)	39/8	111.9±37.3	104.4±36.4	0.35
Protein C (%)	38/7	100.6±42.3	102.1±19.2	0.79
Protein S (%)	21/4	180.4±117.5	58.0±18.1	0.024*
CRP (mg/d) Normal:<0.08mg/dL	29/9	1.59±1.7	0.48±0.65	0.08
ESR (mm/hour)	40/8	29.0±24.8	18.1±15.8	0.23

PT: Prothrombin time, APTT: Activated partial thromboplastin time, vWF: von Willebrand factor, ATIII: Antithrombin III, *: p value with statistical significance

is also under investigation (2, 5, 16, 19, 25-27). APCR caused by factor V Leiden mutation is now recognized as the most prevalent inherited cause of thrombophilia, with a reported prevalence of 2-5% in populations of European descent (13, 17, 28). The frequency of the V Leiden mutation varies greatly in different parts of the world (29). Inheritance of the factor V Leiden mutation appears to be absent in native African, native American and Asian populations (29, 30). In Turkish healthy controls, the prevalence of the factor V Leiden mutation was found to be 7.1% (31). The APTT test is a screening test which provides an assessment of the overall coagulation competence of the intrinsic and common pathways. Not only presence of factor V Leiden but also some lupus anticoagulant antibodies can cause an abnormal APTT-based screening test which reflects a resistance to the anticoagulant activity of exogenous APC (32). Some lupus anticoagulant antibodies may be directed against phospholipid binding proteins involved in the APC inactivation of FVa, which could manifest as acquired APC resistance (5, 19, 21, 33). In our study, APTT was normal in all patients. No test was performed in patients and controls to detect the presence of lupus anticoagulant. Jackson et al. (34) examined APCR and factor V Leiden mutation in a group of 20 patients with IBD and thrombosis, and they found only one patient to be heterozygous for factor V Leiden. Heneghan et al. (19) studied 37 IBD patients (3 had thrombotic events) and 40 healthy controls, and was unable to determine APCR in any of them. Novacek et al. (1) showed that APCR is not associated with IBD, but in its presence the risk of thromboembolism increases. In studies by Helio et al. (35) and Turri et al. (15), the frequency of factor V Leiden mutation in patients with IBD was not significantly different from that in controls. Papa et al. (36) studied 52 IBD (7 had thrombotic events) and 156 healthy controls. They concluded that factor V Leiden mutation did not seem to play a major role in the pathogenesis of IBD or be associated with an increased incidence of thrombotic complications, but with limited data. In another study, 9 of 43 UC and 9 of 20 CD had inherited this mutation (37). On the other hand, Liebman et al. (2) found that 4 of 11 IBD patients with history of thrombosis (36%) and 2 of 5 IBD patients with no history (4%) had APCR and all had factor V Leiden mutation. They concluded that factor V Leiden mutation increases thrombosis risk in IBD patients (2, 38). Koutroubakis et al. (3) studied 48 UC and 36 CD Greek patients with IBD. Six of UC (9.5%) and 2 of CD (8.3%) patients and 3 controls (4.9%) had APCR. Of these, 5 of the UC patients, 2 of the CD patients and 3 controls had factor V Leiden mutation. One patient did not have the mutation. These authors determined that average APCR, but not factor V Leiden mutation prevalence, is significantly higher in IBD patients than controls. Over et al. (37) studied 43 UC and 20 CD Turkish patients with IBD and 36 healthy controls. These authors determined that factor V Leiden mutation was statistically more frequent in CD patients but not in UC patients as compared with controls. Toruner et al. (16) studied 34 UC and 28 CD Turkish patients with IBD and 80 healthy controls. None of the patients had a history of thromboembolism. Heterozygote factor V Leiden mutation was found in 5 (6.25%) control patients and 2 (3.2%) IBD patients. These authors determined that genetic mutations that could increase the thrombosis risk were not different in IBD versus the normal population. Over-Hamzaoğlu et al. (26) examined factor V Leiden mutation in a group of 44 patients with CD (1 had thrombotic events) and 43 healthy controls. They found that 40 of the CD patients had normal factor V genotype, 3 (6.8%) patients showed heterozygous and 1 (2.3%) patient homozygous pattern. Two (4.7%) of the 43 controls showed heterozygous factor V Leiden mutation and 41 had normal factor V genotype. They concluded that the prevalence of factor V Leiden gene mutation was found to be statistically insignificant among CD patients and the control group. In our study, the frequency of factor V Leiden mutation in IBD patients was lower than the frequency in other studies and no healthy controls had factor V Leiden mutation. We also found APCR in 3 of 50 patients without thrombosis history (6%) and in 1 control (2.7%) using plasma test method. Koutroubakis et al. (3) studied APCR and free protein S level in Greek IBD patients and evaluated 48 UC, 36 CD patients and 61 healthy controls. The mean values of free protein S as well as mean APCR were significantly lower in UC and CD patients than in the healthy controls ($p<0.0001$). Seven (5 UC, 2 CD) of 84 IBD patients (8.3%) and 3 of the healthy controls (4.9%) had the factor V Leiden mutation. Conlan et al. (4) studied 7 UC and 1 CD patients and found normal ATIII and no protein C or protein S deficiency. Yılmaz et al. (38) studied 36 UC, 11 CD patients and 17 controls and did not find a significant difference in protein C levels. Free protein S levels were significantly lower in CD and

UC patients than controls ($p<0.0001$). Stadnicki et al. (39) analyzed prothrombotic risk factors in 124 patients with UC as compared with control subjects with other gastrointestinal disorders. They found that platelet level was significantly higher in UC patients compared with control group ($p<0.001$), and APTT was significantly prolonged, respectively, in UC patients compared with the control group ($p<0.05$). In the prospective pilot study, they observed a decrease in plasma antithrombin level and decrease in protein S in approximately 22% of UC patients. They also found that plasma protein C activity was normal in all UC patients, whereas the mean level of protein S was significantly lower in UC patients compared with controls ($p<0.02$). Larsen (14) studied disease activity in 99 IBD patients receiving anti-inflammatory therapy in relation to procoagulant markers, i.e. prothrombin fragments (F1+2), D-dimer and platelet count; anticoagulant markers, i.e. protein C, protein S and antithrombin; and a mediator of inflammation [interleukin (IL)-6]. Coagulation activity and platelet count were increased during active disease in IBD patients compared with those in a state of remission. The IL-6 concentrations were positively correlated with disease activity, but no association with the anticoagulant capacity could be demonstrated except for a decrease in protein C during high disease activity. Jackson et al. (34) did not find any coagulation defect in 52 IBD patients. Deficiency of protein S in IBD has been proposed in the studies of Aadland et al. and Saibeni et al. (40-42). Lake et al. (43) evaluated 12 patients with active disease and in remission. Thrombocytosis, increased levels of fibrinogen, FV and FVIII and decreased antithrombin levels were normalized during remission. Souto and Van Bodegraven et al. found that fibrinogen levels are significantly high in active disease (44, 45). Knot et al. (46) studied 40 IBD patients in remission and could not find significant prethrombotic abnormalities. One patient had thrombocytosis and six had spontaneous thrombocyte aggregation. Thrombocyte factor 4, FVIII, ATIII, plasminogen, $\alpha 2$ antiplasmin, and fibrinopeptide A and $\beta\beta$ were normal in all patients. Conlan et al. (4) found that PTT and APTT were normal in 7 UC and 1 CD patients. This finding showed that patients did not have vitamin K deficiency or plasma coagulation inhibitors. Increased fibrin degradation products and D-dimer levels could not be shown in any of the patients. Souto et al. (44) studied 112 IBD patients (28 CD and 84 UC) and did not find a significant difference between IBD patients and controls for PTT and APTT results. Fibrinogen was higher in active disease than in inactive disease. In our study there was no significant difference between patients and controls or between active disease and remission when PTT, APTT, ATIII, protein C, and FVIII were evaluated. Protein S level was not different in patients and controls, but was lower in 4 remission patients than in 21 active patients. We could not interpret the protein S results because it was evaluated in a very small group. Stevens et al. (47) studied 42 CD, 50 UC and 17 bacterial diarrhea patients and found that serum vWF concentration was significantly higher in the patients versus controls. vWF concentration was also higher in active UC than inactive UC. Additionally, in 5 of 9 patients who became inactivated, vWF concentration was decreased. Active bacterial diarrhea patients had low vWF levels during remission period versus higher levels previously. There was no relation between disease activity and vWF levels in CD. vWF level was higher in active IBD when compared with controls (48). In our study, average vWF levels in active patients were significantly higher than levels in the remission and control groups. Van Bodegraven et al. (45) compared 22 active UC patients with healthy controls. Inflammatory parameters such as CRP, erythrocyte sedimentation rate (ESR), thrombocyte count and fibrinogen levels were found significantly different. There was no significant difference between patients and controls for thrombin-antithrombin complex, fibrin degradation products, and fibrinogen degradation products. In our study, CRP levels and ESR were determined only in patients and there was not a statistically significant difference between active and remission patients. Fibrinogen level was significantly higher in patients and active patients than in controls. Average thrombocyte count was significantly higher in patients than controls and it was also higher in active patients than controls and in patients with remission. Fibrinogen is an acute phase protein, values of which increase with inflammation. High plasma fibrinogen concentrations increase plasma viscosity and activate platelets, both of which may compromise microcirculatory flow within the inflamed intestine (6, 37). In several studies, a significant elevation in fibrinogen has been found in IBD patients (4, 19). We also found that fibrinogen level was significantly higher in patients with IBD than in healthy controls.

In conclusion, APCR is not associated with Turkish IBD patients who have no thromboembolic events. Further, we found that natural coagulation inhibitor deficiency such as protein C, protein S, ATIII and APCR, which could increase the thrombosis risk, were not different in IBD versus the normal population in our study. Our study did not include patients with thrombosis or thrombosis history, so a study of IBD patients with thrombosis will be more illuminating. Further studies are necessary to determine whether a relationship exists between APCR and increased risk of thrombosis in IBD patients with thrombotic complications in the Turkish population. We propose to take into account the fibrinogen level and thrombocyte count increase as inflammation parameters in order to follow the active and remission periods.

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