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Plasma transforming growth factor-β1 level in inflammatory bowel disease

İnflamatuvar barsak hastalıklarında transforming growth faktor-β1 seviyeleri

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Background/aims: *The aim of this study was to evaluate plasma transforming growth factor-β1 concentration in patients with inflammatory bowel disease at different stages of disease activation and to compare these values with those of healthy controls.* ***Methods:*** *A total of 70 patients (31 women) evaluated in the Inflammatory Bowel Disease Clinics of Türkiye Yüksek İhtisas Hospital, Gastroenterology Department, and 20 healthy controls (10 women) were enrolled in the study. Serum samples were obtained from 40 patients with ulcerative colitis (female/male: 18/22, mean age: 41.5±12), 30 patients with Crohn's disease (female/male: 17/13, mean age: 36.9±1.9) and 20 healthy controls (female/male: 10/10, mean age: 32.1±1.7). The control group included normal blood donors without gastrointestinal complaints or a familial history of inflammatory bowel disease. Clinical activity in Chron's disease was measured by Crohn disease activity index and in ulcerative colitis patients by Rachmilewitz endoscopic index. Chron's disease patients with a Chron's disease activity index >150 and ulcerative colitis patients with a Rachmilewitz index ≥4 were accepted to have active disease. Determination of transforming growth factor-β1 level was performed with the enzyme-linked immunosorbent assay.* ***Results:*** *Serum transforming growth factor-β1 levels were measured as: Chron's disease 1133.3±766.5 pg/ml, ulcerative colitis 1362.5±880.6 pg/ml and control group 1230.0±572.7 pg/ml. There were no significant differences between the three groups. In patients with active disease in ulcerative colitis, transforming growth factor-β1 level was measured as 1952.5±543.7, while this value was 772.5±750.5 in patients in remission in ulcerative colitis. There was a significant difference between patients with active ulcerative colitis and remission ulcerative colitis.* ***Conclusions:*** *In inflammatory bowel disease, transforming growth factor-β1 can be used as a marker for differential diagnosis of active ulcerative colitis patients and remission ulcerative colitis patients. Nevertheless, more studies with larger patient groups are necessary.*

Key words: Transforming growth factor-ß1, Crohn's disease, ulcerative colitis, inflammatory bowel disease.

Amaç: *Çalışmamızın amacı inflamatuvar barsak hastalıklarında hastalık aktivasyonu ile TGF-β1 plazma düzeyi arasındaki ilişkiyi sağlıklı kontrol grubu ile karşılaştırmaktır.* ***Yöntem:*** *Çalışmaya alınan 70 hasta daha önce kesin tanısı konmuş 40'ı Ülseratif kolit, 30'u Crohn hastası idi. Ülseratif kolitli hastaların 18'i kadın, 22'si erkek, ortalama yaş: 41.5±12.6 yıl, Crohn hastalarının 13'ü kadın, 17'si erkek, ortalama yaş: 36,9±1,9 yıl idi. Sağlıklı kontrol grubu gastrointestinal şikayeti olmayan, ailesinde inflamatuvar barsak hastalığı öyküsü olmayan sağlıklı kan donörlerinden seçilmiş olup 10'u kadın, 10'u erkek, ortalama yaş: 32.1±1.7 yıl idi. Crohn hastalarının klinik aktivitesi Crohn hastalığı aktivite indeksi ile Ülseratif kolitlilerin aktivitesi ise Rachmilewitz endoskopik indeksi ile değerlendirildi. Crohn hastalığı aktivite indeksi 150'nin üzerinde, Rachmilewitz endoskopik indeksi 4'ün üzerinde olanlar aktif olarak değerlendirildi. TGF-β1 plazma düzeyi ise Elisa yöntemi ile ölçüldü.* ***Bulgular:*** *Serum TGF-β1 düzeyi tüm sağlıklı kontrol grubunda ortalama 1230.0±572.71 pg/ml olup, tüm ülseratif kolitlilerde ortalama 1362.5±880.6 pg/ml, tüm Crohn hastalarında ortalama 1133,3±766,5 pg/ml olup aralarında istatistiksel farklılık yoktu. Ülseratif kolitlilerde ise TGF-β1 plazma düzeyi, aktif hastalarda ortalama 1952,5±543,7 pg/ml , remisyondaki hastalarda ise 772,5±167,8 pg/ml olup remisyondaki ülseratif kolitliler ile aktif ülseratif kolitliler arasında da istatistiksel olarak anlamlı farklılık vardı.* ***Sonuç:*** *İnflamatuvar barsak hastalığında serum TGF-β1 düzeyi aktif Ülseratif kolitli hastalarda hastalık aktivitesi ilişkili bulunmakla beraber konuyla ilgili daha büyük hasta grupları ile çalışmalar yapılmasına ihtiyaç vardır.*

Anahtar kelimeler: TGF-ß1, Crohn hastalığı, Ülseratif kolit, İnflamatuvar barsak hastalıkları

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic intestinal inflammatory disease consisting of two forms of chronic intestinal inflammation: ulcerative colitis (UC) and Crohn's disease (CD).

The pathogenesis of IBD remains unclear. The etiology of IBD is multifactorial: genetic predisposition, unregulated intestinal immune response, environmental factors, diet, and infections have

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been suggested. IBD may also be related to diminished ability of mucosal protection and regeneration following injury. These processes are regulated by intercellular signalling through a complex network composed of cytokines, growth factors and other active substances responsible for cell proliferation and differentiation as well as regulation of immune response (1-3). Intestinal inflammation in experimental models and perhaps in humans may result from an imbalance between pro-inflammatory and anti-inflammatory factors involved in the mucosal immune response (4).

Transforming growth factor-ß (TGF-ß) belongs to a family of multi-functional polypeptides produced by lymphoid and non-lymphoid cells. It has five different isoforms (5). TGF-ß1 has confirmed effects on cell proliferation, immunosuppression and wound healing (6). Its participation in the pathogenesis of diseases related to fibrosis has been established recently (7). Moreover, involvement of this molecule in the pathogenesis of cancer, autoimmune disorders and atherosclerosis suggests its possible use as a prognostic indicator (8). The demonstration of enhanced expression of TGF-ß1 in human colonic mucosa of UC patients might indicate a role of this molecule in the pathogenesis of the disease (9). Increased TGF-ß expression is shown in the affected mucosa of patients with UC and CD in the active phase of the disease (9).

The aim of this study was to evaluate plasma TGF-ß1 concentration in patients with IBD at different stages of disease activation and to compare these values with those of healthy controls.

MATERIALS AND METHODS

A total of 70 patients (31 women) evaluated in the IBD Clinics of Türkiye Yüksek İhtisas Hospital, Gastroenterology Department, and 20 healthy controls (10 women) were enrolled in the study. The control group included normal blood donors without gastrointestinal complaints or a familial history of IBD.

Patients diagnosed as CD or UC by endoscopy/histopathology and clinical evaluation, and who did not use steroids, sulfasalazine group, azathioprine or anti-inflammatory drugs for at least one month, were included in our study.

Age, sex, disease localization, and the nature of CD (inflammatory, stenosing or fistulizing) were recorded. Patients with CD and UC were subgrouped according to the disease state as active or in remission. In order to define activation and remission of the disease state, Crohn's disease activity index (CDAI) was used for CD patients and Rachmilewitz endoscopic index for UC patients. CD patients with a CDAI >150 and UC patients with a Rachmilewitz index ≥4 were accepted to have active disease (10,11). C-reactive protein (CRP), fibrinogen, platelet count, white blood cell count, sedimentation rate and TGF-ß1 level were measured in all patients. TGF-ß1 levels were also assessed in the control group.

Plasma TGF-ß1 levels were measured using enzyme linked immunosorbent assay (ELISA) method (Bender Medical Systems, Vienna, Austria).

Statistical Analysis

All data were collected and analyzed with Microsoft Excel 97 software (Microsoft Corporation). Values were expressed as mean ± standard error of the mean (SEM). The significance of the difference was calculated by two-tailed Student's t-test. For correlation analysis, the Pearson product moment correlation was used and linear regression was performed. Values of $p<0.05$ were considered to be significant.

RESULTS

Seventy patients with known IBD (40 UC, 30 CD) were included in the study. The mean follow-up periods of the patients were 68.85±87.34 months for UC patients and 39.67±10.41 months for CD patients. Twenty (50%) of the patients with UC were in remission, and 20 were in the active pha-

Table 1. General characteristics of the cases included in the study

	UC (n=40)	CD (n=30)	Healthy controls (n=20)
Follow-up period (months)	68.85±87.34 (8-489)	39.67±10.41 (2-168)	
Age (years)	41.55±12.04 (20-61)	36.9±1.9 (18-63)	32.1±1.7 (21-42)
Female	18	13	10
Male	22	17	10
Distal type UC	7 (17.5%)		
Left type UC	12 (30.0%)		
Ext + Pancolitis UC	21 (52.5%)		
Remission	20 (50.0%)	15 (50.0%)	
Active state	20 (50.0%)	15 (50.0%)	
Small intestine		11 (36.66%)	
Colon		2 (6.66%)	
Small intestine + colon		17 (56.66%)	
Inflammatory		14 (46.66%)	
Stenosing		9 (30.00%)	
Fistulizing		7 (23.33%)	

se. Seven patients (17.5%) with UC had distal type localization, 12 (30.0%) had left side localization, and 21 (52.5%) had extensive + pancolitis.

Fifteen (50.0%) of the CD patients were in remission and 15 were in the active phase. Eleven CD patients (36.7%) had small intestine involvement, 2 (6.7%) colon, and 17 (56.7%) small intestine + colon. Fourteen (46.7%) of the CD patients were inflammatory type, 9 (30.0%) were stenosing, and 7 (23.3%) fistulizing type. The characteristics of the patients included in the study are summarized in Table 1.

Ten of the healthy volunteers were women, with a mean age of 32.1±1.7 years.

C-reactive protein, sedimentation rate, white blood cell count, fibrinogen level, platelet count, and TGF-ß1 level of all the patients are shown in Table 2. CRP, sedimentation rate, white blood cell count, fibrinogen level, platelet count, and TGF-ß1 value of the patients with CD are shown in Table 3.

In CD patients, there was a statistically significant difference in terms of white blood cell count and sedimentation rates between cases with active disease and those in remission (p=0.010 and p=0.011, respectively).

C-reactive protein, sedimentation rate, white blood cell count, fibrinogen level, platelet count, and TGF-ß1 level of patients with UC are shown in Table 4.

In UC patients, there was a statistically significant difference in terms of platelet count and TGF-ß1 between patients in the active phase and patients in remission (p=0.017 and p=0.000, respectively).

While there was a difference in CD in the active phase and in remission in terms of white blood cell count and sedimentation rate, there was no difference in these parameters in UC patients, but there was a significant difference in terms of platelet count and TGF-ß1 in cases with active disease and those in remission.

The mean TGF-ß1 plasma level in the UC group was 1362.5±880.6 pg/ml and it was not statistically significantly different compared to that of healthy controls (1362.5±880.6 pg/ml vs. 1230.0±572.713 pg/ml; p=0.544).

The mean TGF-ß1 plasma level in UC cases in remission was 772.5±750.5 pg/ ml, and this was lower than that of the healthy controls, with a statistically significant difference (772.5±750.522 pg/ml vs. 1230±572.713 pg/ml; p=0.037). The mean TGF-ß1 plasma level in patients with active UC was 1952.5±543.7 pg/ml and it was higher than those of both the healthy control group and the UC cases in remission, and the difference was statistically significant (1952.5±543.7 pg/ml vs. 1230±572.713 pg/ml vs. 772.5±167.882 pg/ml; p=0.000 vs. p=0.000) (Table 5).

Table 2. C-reactive protein, sedimentation rate, white blood cell count, fibrinogen level, platelet count, and TGF-ß1 in all patients

	CD	UC	Healthy control
WBC (U/L)	7931±3255	8975±3202	
CRP (mg/L)	3.7±4.5	1.0±1.2	
Sedimentation rate (After 1 h) (mm)	26.2±16.4	13.8±10.7	
Fibrinogen level (mg/dl)	3.1±0.8	2.7±1.0	
Platelet count (x 10^3 U/L)	404±139	366±121	
TGF-ß1 (pg/ml)	1133.3±766.5	1362.5±880.6	1230.0±572.7

WBC: White blood cell. CRP: C-reactive protein.

Table 3. C-reactive protein, sedimentation rate, white blood cell count, fibrinogen level, platelet, and TGF-ß1 level in patients with Crohn's disease

	Active state	Remission	p
WBC (U/L)	9473±3979	6390±1012	0.010
CRP (mg/L)	4.8±3.9	2.8±4.9	0.310
Sedimentation rate (After 1 h) (mm)	35.8±17.1	18.7±11.6	0.011
Fibrinogen level (mg/dl)	3.3±0.99	3.0±0.7	0.328
Platelet count (x 10 3 U/L)	446±180	365±77	0.136
TGF-ß1 (pg/ml)	1310.0±719.9	956.6±759.0	0.213

WBC: White blood cell. CRP: C-reactive protein.

Table 4. C-reactive protein, sedimentation rate, white blood cell count, fibrinogen level, platelet, and TGF-ß1 level in patients with ulcerative colitis

	Active state	Remission	p
WBC (U/L)	10078±3713	7873±2169	0.270
CRP (mg/L)	1.4±1.4	0.5±0.5	0.240
Sedimentation rate (After 1 h) (mm)	15.3±12.4	12.4±8.9	0.403
Fibrinogen level (mg/dl)	3.0±1.2	2.4±0.5	0.092
Platelet count (x 10^3 U/L)	411±141	321±77	0.017
TGF-ß1 (pg/ml)	1952.5±543.7	772.5±750.5	0.000

WBC: White blood cell. CRP: C-reactive protein.

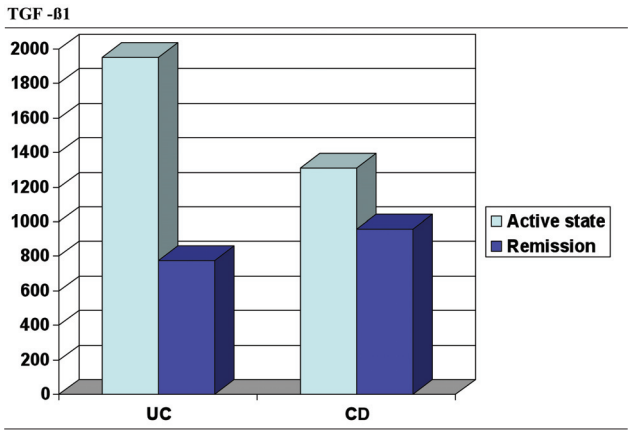
The mean TGF-ß1 plasma level in all CD patients was 1133.3±766.5 pg/ml, and it was not significantly different from that of the healthy controls (1133.3±766.579 pg/ml vs. 1230.0±572.713 pg/ml; p=0.633). In cases with active CD, the mean TGF-ß1 plasma level was 1310.0±719.9 pg/ml, and there was no significant difference when compared to the healthy control group (1310.0±719.9 pg/ml vs. 1230±572.713 pg/ml; p=0.716).

The mean TGF-ß1 plasma level in CD patients in remission was 956.6±759.0 pg/ml, and again there was no significant difference when compared to the control group (956.6±759.0 pg/ml vs. 1230±572.713 pg/ml; p=0.245).

There was no statistically significant difference between active CD patients and those in remission in terms of plasma TGF-ß1 levels (1310.0 ± 719.921 pg/ml vs. 956.67±795.044 pg/ml; p=0.212) (Table 5).

In all CD patients (both with active disease and in remission), there was no statistically significant difference in terms of plasma TGF-ß1 levels. Additionally, plasma TGF-ß1 levels did not differ between CD patients and healthy controls.

Table 5. TGF-ß1 level (pg/ml) in patients with Crohn's disease and ulcerative colitis



No difference was found when the plasma TGF-ß1 levels of all UC cases were compared to all CD cases (p=0.259).

When the relationship between acute phase reactants and TGF-ß1 was evaluated, there was a mild correlation between CRP and TGF-ß1 in patients with UC.

Evaluation of all cases with active disease or in remission showed that the acute phase reactants-white blood cell count, platelet count and plasma TGF-ß1 levels- were statistically higher in active patients than in those in remission (p<0.005).

Evaluation of UC cases as active and in remission revealed that among acute phase reactants, the platelet count and plasma TGF-ß1 levels were statistically higher in active patients compared to those in remission (p<0.05).

Evaluation of the CD cases as active and in remission showed that among the acute phase reactants, the white blood cell count and sedimentation rates were statistically higher in active patients compared to those in remission (p<0.05).

DISCUSSION

It is known that TGF-ß1 plays an important role in the pathophysiology of IBD (1). In IBD, TGF-ß1 is produced and secreted from the cells in the lamina propria and the epithelium of the small bowel and colon (12). TGF-ß1 controls proliferation and differentiation of intact epithelial cells, and plays a role in wound healing and increase in fibrosis during inflammation. It enhances the production of extracellular matrix by intestinal cells and fibroblast-mediated contraction of the collagen matrix, and also regulates the function of leukocytes and endothelial cells as well as their products (13).

Because of the effect on fibrosis, TGF-ß1 has also been implicated in stricture formation and muscle hypertrophy occurring sometimes as a complicati-

on in IBD (14, 15). Additionally, TGF-ß1 affects the inflammation in the bowel through induction of cyclooxygenase-2, and the subsequent increase in prostaglandin production (16).

The general opinion in IBD is that plasma TGF-ß1 levels increase parallel to the increase in cytokine secretion due to inflammation (17). In our study, we evaluated plasma TGF-ß1 levels in active IBD patients and in those in remission, and found that levels were statistically higher in active UC cases compared to those in remission and the control group.

We found no relationship between TGF-ß1 and disease activation in CD. In the literature, there are some studies relating CD and TGF-ß1 during activation (9), while other studies reported no relationship between TGF-ß1 levels and active UC and CD (18). Del Zotto et al. (5) reported that cytokine activation in UC and CD takes place through different cascades and that the effect of these cytokines on TGF-ß1 production differs. It has been demonstrated that CD is a Th-1-orientated inflammation in which the cells overproduce cytokines such as interleukin (IL)-12 and interferon (IFN)-γ, while in UC there was an increase in IL-5 (a Th-2 cytokine) production with normal levels of IFN-γ (19, 20).

Studies in the murine system have shown that differentiation of TGF-ß1 producing cells is negatively and positively affected by the presence of IFN-γ and IL-4, respectively (21). Therefore, it is quite possible that the presence of an established Th-1 response as in CD may prevent *in vivo* expansion of TGF-ß1-producing cells. On the other hand, the presence of Th-2 type cytokines, as in UC, may favor the emergence of TGF-ß1-producing cells. In our study, we found no difference in the TGF-ß1 levels in CD cases compared to the control group, but a difference was found in the active UC cases compared to the cases in remission and the control group. This can be due to the production of TGF-ß1 through different cascades with an increase of IFN-γ in CD (5).

It is known that plasma TGF-ß1 levels are affected by steroid use, and there are also studies implying that the plasma level of TGF-ß1 is affected by sulfasalazine and other anti-inflammatory drugs (22, 23). For this reason, the patients included in our study were those who for various reasons including patient noncompliance, economic factors or social security problems had not received any kind of treatment at all.

C-reactive protein, sedimentation rate, white blood cell count, and platelet count are known markers of disease activation in IBD, but their correlation with disease activity is reported to be different in different studies (24-29). In our study, there was a weak correlation in all UC cases in terms of CRP and TGF-ß1 levels, whereas no correlation was established between the other parameters and TGF-ß1.

The evaluation of the patients with active disease and those in remission revealed that platelet count was higher in UC patients with active disease compared to those in remission. On the other hand, white blood cell count and sedimentation rate were found to be higher in CD patients with active disease compared to those in remission.

The small study group is one of the shortcomings of our study; the reliability of our results would be better with a larger patient population.

In conclusion, in IBD, TGF-ß1 can be used as a marker for differential diagnosis of active UC patients and those in remission. Nevertheless, more studies with larger patient groups are necessary.

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