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# Possible Role of TNF-α, IFN-γ, FAS/APO1 in the Etiopathogenesis of Lichen Planus

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**Keywords:** Lichen planus, TNF-a, IFN-γ, FAS/APO1

**Abstract**

**Background:** Although the cause of lichen planus is not completely clear, there is strong evidence suggesting that the underlying pathologic mechanism is immunologic.

**Objective:** The aim of this study was to show the effect of apoptotic markers in the etiopathogenesis of lichen planus.

**Subjects and Methods:** Twenty-one patients diagnosed with lichen planus clinically and histopathologically were included in the study. The control group included 12 healthy subjects. TNF-α, IFN-γ and Fas/APO levels in tissue and serum were measured using ELISA kits.

**Results:** No significant difference was found between the patient and control groups with regard to serum TNF-α and Fas antigen levels, but IFN-γ level was significantly lower in the patient group than in the control group (p=0.003). No significant difference was found between tissues with lesion and control tissues in terms of TNF-α and IFN-γ (p=0.178, p=0.190), but Fas antigen was statistically significantly higher in the patient group than the control group (p=0.001). No difference was found between non-lesional tissues in the patient group and control tissues with regard to TNF-α, Fas antigen and IFN-γ levels (p=0.575, p=0.238, p=0.085). No significant difference was found between the tissues with and without lesions in the patient group with respect to TNF-α values (p=0.448), but Fas antigen was established to be statistically significantly higher in the tissues with lesion than those without (p=0.000) while IFN-γ was significantly higher in the tissues without lesion (p=0.014).

**Conclusion:** In lichen planus, while IFN-γ tissue levels were low and Fas antigen tissue levels were high, serum TNF-α levels were found to be low. These parameters support the pathogenesis of the disease and the results of previous studies.

## Introduction

Although there are many theories attempting to account for the etiology of lichen planus (LP), it remains unknown. Among the different opinions advanced, infectious agents, neurological changes, psychological stresses, and genetic and immunologic factors are mentioned as probable causes. It is accepted that T lymphocytes play the primary role in the pathogenesis.Th lymphocytes are divided into different subtypes according to their functions and cytokines that they release in the immune system. Th1 cells typically pro-

**Tablo 1.** TNF-α, IFN-γ, FAS/Apo-1 Levels in the Serum of Patient and Control Groups *P≤ 0.05

| | Patient group | Control group | P |
|---|---|---|---|
| **TNF-α** | 13.86±2.92 | 16.89±13.36 | 0.653 |
| **IFN-γ** | 6.97±1.37 | 8.60±1.16 | 0.003* |
| **FAS/APO1** | 2.14±0.57 | 2.26±0.36 | 0.303 |

**Table 2.** TNF-α, IFN-γ, FAS/Apo-1 Levels in the Lesional Tissue in the Patient Group and in the Control Group *P≤ 0.05

| | Tissues with lesion | Normal skin | P |
|---|---|---|---|
| **TNF-α** | 42.97±20.35 | 32.39±14.27 | 0.178 |
| **IFN-γ** | 33.77±19.25 | 37.47±10.96 | 0.190 |
| **FAS/APO1** | 4.91±1.77 | 2.30±1.72 | 0.01* |

**Table 3.** TNF-α, IFN-γ, FAS/Apo-1 Levels in the Lesional Compared to Non-Lesional Tissues in the Patient Group *P≤ 0.05

| | Tissues with lesion | Non-diseased tissues | P |
|---|---|---|---|
| **TNF-α** | 42.97±20.35 | 37.63±20.36 | 0.448 |
| **IFN-γ** | 33.77±19.25 | 50.69±20.27 | 0.014 |
| **FAS/APO1** | 4.91±1.77 | 2.89±1.76 | 0.000* |

**Table 4.** TNF-α, IFN-γ, FAS/Apo-1 Levels in the Non-Lesional Tissues of Patient Group and Control Group

| | Non-diseased tissues | Normal skin | P |
|---|---|---|---|
| **TNF-α** | 37.63±20.36 | 32.39±14.27 | 0.575 |
| **IFN-γ** | 50.69±20.27 | 37.46±10.96 | 0.085 |
| **FAS/APO1** | 2.89±1.76 | 2.30±1.72 | 0.238 |

duce interferon (IFN)-γ and tumor necrosis factor (TNF)-α which are involved in macrophage activation [**1**]. TNF-α is the major mediator of inflammation, which actions directed towards both tissue destruction and recovery.While inducing death of diseased cells at the site of inflammation, TNF stimulates fibroblast growth [**2, 3**]. Th1 cytokines, cytotoxic CD8+ T cells are activated and trigger basal keratinocytes apoptosis, possibly via secreted TNF-α, resulting in the clinical and histological apperance of LP [**4**]. Th2 cells produce interleukin (IL)-4, IL-5 and IL-13. A third subset is called the Th17 because its signature cytokine is IL-17 [**1, 3**]. T lymphocyte activation occurs through Th-1 induction of some viral, bacterial, cellular and pharmacological agents, Langerhans cells and keratinocytes [**5, 6**]. In studies using monoclonal antibodies to subgroups of T lymphocytes, it has been shown that the predominant cell type in the dermal infiltrate is Th-1 [**5, 6, 7, 8, 9, 10**]. As IFN-γ and TNF-α release are dominant in immunological processes, LP is a disease characterized by type 1 cytokine pattern. The interaction of antigen presenting cells with T lymphocytes is cytotoxic for keratinocytes. Both CD4+ and CD8+ T lymphocytes are found in LP lesions. In the dermis, CD4+ T cell infiltration is mostly found, and it gives rise to epidermal cell damage by activating CD8+ cytotoxic T cells [**8, 9, 10, 11, 12**].

Apoptosis is cell death that can be controlled genetically, and the regulation of apoptosis is dependent on interactions between effector and suppressor molecules. It occurs via the activation and inactivation of many proteins, which are gene products, and it may induce or inhibit this process [**8**]. This event takes place via two different pathways, namely perforin-granzyme mediated by CD8+ cytotoxic T lymphocyte (CTLs) and Natural killer (NK) cells and Fas receptor (Fas R)/Fas ligand (Fas L) pathway. Recently, it has been shown that perforin (pore forming protein) and granzymes, which are the major components of cytoplasmic granules of CTLs and NK cells, are influential in CTL- and NK-cell mediated apoptosis. The Fas system is involved in activation-induced suicide of T cells and downregulation of immune reaction [**13**].

Fas R (Apo-1 or CD 95) is the cell surface protein member of the TNF/nerve growth factor receptor family. It may be expressed in both lymphoid and non-lymphoid cells. Fas L is a member of the TNF family and is expressed in mature tissue especially from neutrophils and active lymphocytes. The Fas R/Fas L system triggers apoptosis and causes apoptotic dysfunction, playing a role in the pathogenesis of many autoimmune diseases. Fas R and Fas L have membrane-dependent and soluble forms. The soluble form of Fas (sFas) may inhibit T lymphocyte-mediated cytotoxicity in vitro and may modify lymphocyte formation and proliferation in the response to self antigen [**6, 7, 8, 9, 10, 11, 14, 15**].

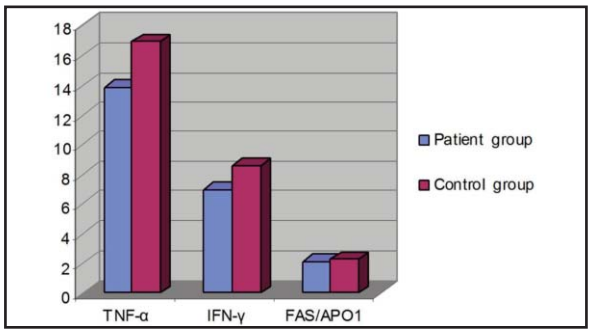


**Figure 1.** TNF-α, IFN-γ, FAS/Apo-1 levels in the serum of patient and control groups *P≤ 0.05

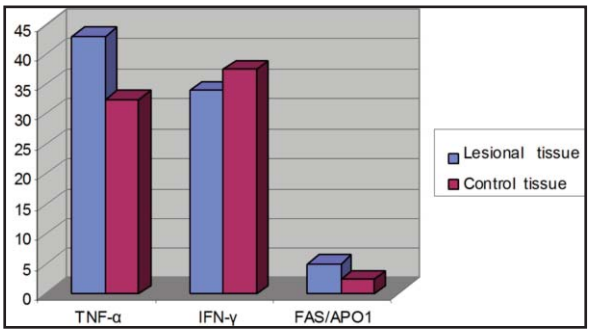


**Figure 2.** TNF-α, IFN-γ, FAS/Apo-1 levels in the lesional tissue in the patient group and in the control group

The aim of the present study was to investigate the role of TNF-α, IFN-γ and Fas R in the etiopathogenesis of LP. Therefore, the levels of proinflammatory cytokines and Fas/Apo-1 were established in serum and in tissues with and without lesions in patients with LP and in a control group by using enzyme-linked immunosorbent assay (ELISA) method, and the results were compared.

## Materials and Methods

Twenty-one patients aged between 20-81 years who referred to the Dermatology Department of Kırıkkale University Faculty of Medicine and were diagnosed with LP clinically and histopathologically were included in the study. The control group included 12 healthy subjects between the ages of 33-55 years.

Inclusion criteria of the study were as follows: age older than 18; diagnosis of LP clinically and histopathologically; no sexual discrimination; no corticosteroid treatment within the last four months systemically or within the last one month topically; no history of lichenoid drug eruption; no known autoimmune or malignant disease; and voluntary participation.

The study was approved by the Ethics Committee of Kırıkkale University Medical Center, Kırıkkale, Turkey.

*Study protocol:* Diagnosis of LP in patients based on dermatological examination in the clinic was subsequently confirmed histopathologically. Age, sex, lesion location, duration of disease, association with systemic diseases, use of systemic or local drugs, association with autoimmune diseases, and family history of a similar disease were recorded for all patients. Routine biochemical tests were carried out and fasting blood sugar and hepatitis markers (hepatitis A, B, C) were investigated.

Skin samples were taken from the lesional skin of the patients and from healthy sections using 4 mm punch biopsy device and were frozen with liquid nitrogen and kept at deep freeze at –70°C. Venous blood (5 cc) was withdrawn from all participants in the patient and control groups.

*Statistical analysis:* All categorical data of the patient and control groups (categorical and numerical) were evaluated using SPPS for Windows 8.0 standard version. The differences between ages in the groups were evaluated with Mann-Whitney U test and differences between sexes with chi-square test. The comparisons of the serum in control and patient groups, of lesional tissue and control tissue, and of non-lesional tissue in the patient group and control tissue were carried out with Mann-Whitney U test; comparison of tissues with and without lesions was done with paired-t test. P value <0.05 was considered to indicate statistical significance.

## Results

This study was carried out with 21 patients diagnosed with LP clinically and histopathologically [7 female (33.3%), 14 male (66.7%)] and 12 controls (6 female, 6 male, 50%). Ages of the patients ranged between 20-81 years (mean: 50.33±13.61). The duration of disease varied between 1-36 months (mean: 7.76±9.40). Ages of the controls ranged between 33-55 years (mean: 46.33±7.91). There was no statistically significant difference between patient and control groups in terms of age or sex (p=0.358, p=0.465, respectively).

There was no involvement of scalp skin in patients. In 9 (42.8%) patients skin involvement, in 8 (38%) skin and oral mucosa involvement, in 2 (4.8%) skin and genital region involvement (in males involvement of glans penis), in 1 (2.4%) skin, oral mucosa and genital region involvement, and in 1 (2.4%) skin and nail involvement were present. No association with systemic diseases was established in our patients.

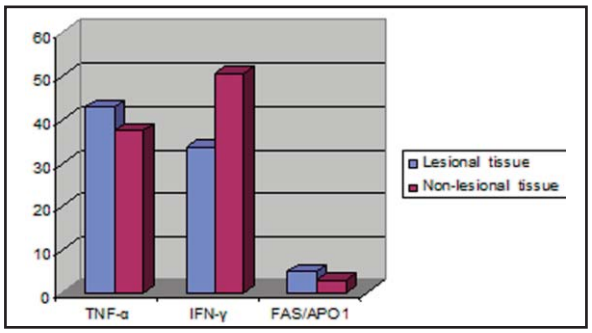


**Figure 3.** TNF-α, IFN-γ, FAS/Apo-1 levels in the lesional compared to non-lesional tissues in the patient group *P≤ 0.05

In patients with LP, serum TNF-α levels were low compared to the control group, but the difference was not statistically significant. The values of Fas R were similar between the two groups. Serum IFN-γ level was statistically significantly lower in the patient than in the control group (**Table 1, Figure 1**).

No significant difference was found between lesional tissues and control tissues in terms of TNF-α and IFN-γ but Fas R was statistically significantly higher in the patient group compared to the control group (**Table 2, Figure 2**).

In the patient group, comparison of lesional versus non-lesional tissues demonstrated that Fas R was statistically significantly higher in the tissues with lesion than in those without while IFN-γ was found to be statistically significantly higher in the tissue without lesion. No significant difference was found between the tissues with and without lesion in the patient group with respect to TNF-α values (**Table 3, Figure 3**).

No difference was found between non-lesional tissues in the patient group and control tissues with regard to TNF-α, Fas antigen and IFN-γ levels (**Table 4**).

## Discussion

Recent studies have suggested that keratinocyte apoptosis in LP may be triggered by TNF-α directly or by causing the migration of cytotoxic T lymphocytes to the lesion region. Comparison of LP epithelium with normal controls has demonstrated that the rate of apoptosis increased, and many studies have been carried out on this issue [**15**].

*Juretic* et al. studied TNF-α and IL-6 in salivary in 19 groups with oral lichen planus (OLP), with malignity and with perfect health through ELISA method and found these proinflammatory sitokins significantly higher than in the control group [**2**]. *Piccinni* et al. studied Th 17, Th0 and Th2 sitokin expressions in mucosa biopsy taken from 14 patients with OLP. They demonstrated that Th17 and Th0 type molecules are increased in erosive OLP, whereas Th2-types molecules predominate in reticular oral LP. They demonstrated that Th17 and Th0 type molecules are increased in erosive OLP, whereas Th2-types molecules predominate in reticular oral LP. They found INF-γ and TNF-α expression in erosive OLP significantly higher than in the control group [**12**]. *Zhou* et al. examined IL-2, 4, 10 and IFN-γ concentrations from peripheral blood from 22 cases with OLP via ELISA method. They found IFN-γ and IL-2 levels significantly higher compared with the control group [**4**]. *Zhang* et al. researched the levels of IL-18 sitokins that induce IFN-γ and TNF-α sitokins from T-cells and which regulate up Th1 sitokins in salivary and serum in 103 Chinese population with OLP, and found the level of IL-18 significantly higher [**16**]. In the same population, *Lui* et al. studied IFN-γ and TNF-α sitokins in the same material and found the levels of IFN-γ lower than in the control group [**17**]. *Pekiner* et al. examined IFN-γ, TNF-α, IL-2, IL-4, IL-5, IL-10 levels with flow cytometry in serum in 30 cases with OLP, but encountered no significant result in IFN-γ, TNF-α, IL-4, IL-5 levels [**18**]. A similar study was conducted by *Kalogerakou* et al. while a significant decline was demonstrated in IFN-γ level, no difference was found in TNF-α level compared with the control group [**19**]. *Lui* et al. found a significant decrease in IFN-γ level in patients with OLP [**20**].

*Bloor* et al. investigated the expression of MIB-1, Bcl-2 and bax in 26 OLP patients immunohistochemically and demonstrated that epithelial disruption by the lymphocytic infiltration is associated with significantly higher apoptotic counts, but there appears to be no correlation between the frequency of apoptosis and proliferative activity [**7**].

*Erdem* et al. investigated the TNF-α level in patient serum with ELISA in 40 patients with LP and found the levels in the patient group to be significantly higher than those in the control group. In the same study, when cases were evaluated with respect to oral involvement, no significant difference was found between the patients with oral involvement and those without [**21**].

*Yamamato* et al. investigated the level of TNF-α in the serum of 26 patients with LP using ELISA and found that the level was slightly increased only in 9 cases. Marked increase was not observed in any case, and they were not able to explain the pathogenesis of the disease with these results [**22**].

In the report of *Sugerman* et al., serum TNF-α level was found to be above normal in 2 cases with OLP, while it was within normal range in 9 cases [**23**].

*Simon* et al. investigated TNF-receptor (TNF-R) I and II expression immunohistochemically in lesional tissue and with ELISA in serum in 15 patients with LP and compared the findings with 10 healthy controls. They detected no TNF-R II expression in lesion tissue and in the control group. TNF-R I expression was found to be prominent in basal keratinocytes of the skin with lesion and all layers of epidermis in the control group. When the same parameters were evaluated in serum, they were found to be significantly higher in the patient group compared to control group [**24**]. *Zenous* et al. found the TNF-α level in serum was significantly higher than the control group [**25**].

In the study of *Muraki* et al. on 20 patients with OLP, lesional tissue in oral mucosa was stained with Fas D antibody and Fas+ staining was observed in 18 patients. It was established that Fas antigen yielded intensive immunoreactivity in the surface and spinous layers [**26**].

*Sklavounou-Andrikopoulou* et al. investigated the level of serum TNF-α, sFas/Apo-1 and Bcl-2 levels and found the values of TNF-α and Fas/Apo-1 to be significantly higher in the patient group than the control group [**11**]. In the present study, serum Fas/Apo-1 values were found to be comparable in patient and control groups and TNF-α values were lower in the control group, while tissue Fas/Apo-1 expression was significantly higher than control group and tissues without lesion. *Neppelberg* et al. evaluated CD3, CD4, CD8, Fas R and Fas L positive signals in 18 OLP cases using the end-labelling method (TUNEL) intraepithelially and subepithelially. They demonstrated that the expression of Fas R/Fas L was prominent in OLP. In the epithelium, the Fas R/Fas L expression was more abundant in the basal cell area compared to the suprabasal cell layer [**13**]. *Shen* et al. studied the expression of Fas/Fas L in 50 OLP and 10 control group with immunohistochemical TUNEL method, and determined Fas expression to be ≥ 50 % in 34/50 cases. They found it to be more significant compared with that in the control group (p=0.000). They also determined that FasL expression was significant in the patient group (p= 0.007) [**27**].

Our findings were in accordance with those of *Muraki* et al., *Sklavounou-Andrikopoulou* et al., *Balvinder* et al. and *Neppelberg* et al. Since local cytokine release is incriminated in the damage to basal keratinocytes, we think that the findings related to Fas/Apo-1 are consistent with the pathogenesis of the disease [**11**]. In our study, we found the TNF-α level in serum to be lower in the patient group than the control group. When cases were considered according to sex and clinical type, it was established that there was no significant difference between sexes, and LP with local involvement was much more common than that with generalized involvement in the patient group. While the findings of our study regarding TNF-α levels are not in agreement with those of *Erdem* et al., *Simon* et al., *Sklavounou-Andrikopoulou* et al., *Juretic* et al., *Piccini* et al., *Zhou* et al. and *Zhang* et al. they are in accordance with the findings of *Yamamoto* et al., *Sugerman* et al. and *Kalogerakou* et al. The difference in the serum levels of TNF-α may be related to several factors, namely:

1. As TNF is released from many cells, the cellular source of the activity is not known.

2. Clinical phase of the disease and TNF levels correlate, hence cytokines may be detected only in the active period of the disease.

3. Its half-life in the serum is very short (6-30 minutes). The levels of TNF–α may decrease rapidly after bonding to soluble TNF–α receptor or protein or due to renal excretion. Therefore, it is difficult to determine the biological activity of TNF-α [**23**].

*Sklavounou* et al. investigated TNF-α expression and apoptotic markers by immunohistochemical method in 22 cases with OLP and established that in 5 of 22 cases TNF expression was negative, in 11 staining was between 15-40% and in 6 cases it was over 40%. Investigators considered 11 cases with slight stai-

ning as positive, and compared them with a control group and found TNF-α expression to be significantly higher. In the present study, TNF-α levels in the tissue were evaluated quantitatively both in patients and a control group. Since the aforementioned study made a qualitative evaluation and considered slight staining as positive, we think that our findings are consistent with theirs [**8**].

In the study of *Fayyazi* et al. on 15 patients with LP, it was reported that all cells expressing IFN-γ were CD3+ T lymphocytes. They also demonstrated that proinflammatory cytokines such as IFN-γ and IL-6 were produced not only in active T lymphocytes but also in keratinocytes in basal and suprabasal layers [**28**]. They reported that TNF-α and IFN-γ may lead to liquefaction degeneration in basal membrane and basal keratinocytes.

*Khan* et al. investigated TNF-α, TNF R1, IFN-γ, CD4 and CD8 levels using ELISA in standard immunohistochemical and tissue supernatants in 5 patients with OLP. In their study, 20-40% of subepithelial infiltrating T cells were found to be CD4+ T cells, which are responsible for IFN-γ and IL-2 secretion. In various reports, it has been emphasized that IFN-γ and TNF-α are proinflammatory cytokines, that TNF-α reduces IFN-γ secretion, and that these cytokines play an active part in the clinical type and disease activity in LP. Although the findings obtained in the above-mentioned study were not compared with a control group, it has been reported that TNF-α expression increased whereas IFN-γ expression decreased [**29**].

In the present study, TNF-α levels were found to be higher in tissue with lesions than both the tissues without lesion and control tissue, but the difference was not statistically significant. If our results obtained with quantitative methods were evaluated qualitatively, however, they could be determined more significant statistically. In our study, when IFN-γ level was evaluated, it was found to be significantly lower in the serum of the patient group compared with the control group (p=0.003). When IFN-γ levels were evaluated in the tissue, they were found to be significantly lower in the region with lesions than those without lesions (p=0.014). No significant difference was found between lesion region and controls (p=0.190). Cytokine levels in the lesion region were significantly lower than in the control group. While our study was not similar with *Pekiner* et al., *Piccini* et al., *Zhou* et al. and *Zhang* et al's studies, was similar with *Lui* et al. and *Kalogerakou* et al.'s studies. We consider the lack of significant difference (p=0.085) between tissue samples without lesion and the control group to be meaningful. The data obtained in our study were consistent with both the pathogenesis of the disease and the above study.

*Carrozzo* et al. investigated the polymorphism of IFN-γ and TNF-α using polymerase chain reaction (PCR) in 44 cases with LP and reported that these cytokines influence the clinical type of the disease and contribute to the predisposition to LP, and they stressed that their results contradicted those of previous studies [**30**]. *Yamamoto* et al. evaluated the serum IFN-γ levels of 30 patients diagnosed with OLP by enzyme immunoassay method and found serum IFN-γ production to be slightly lower than in the control group. Likewise, in the present study, serum IFN-γ levels were found to be significantly lower in patients with LP than in controls [**31**].

In conclusion, according to our findings, IFN-γ tissue levels were low and Fas antigen tissue levels were high in LP. In this study, although serum TNF-α levels were found to be low, other parameters supported the pathogenesis of the disease and the results of previous studies. We believe that larger studies in which apoptotic markers are measured with more sensitive methods may yield sounder results. The clarification of apoptotic markers and their function, which is regarded as the cornerstone of the pathogenesis of LP, may shed further light on the pathogenesis of this disease.

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