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Serum fibroblast growth factor 2 level in psoriasis; relationship with disease severity

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Abstract

Aim: Psoriasis is a disease characterized by chronic inflammation of the skin and small joints that causes serious deterioration in quality of life. Inflammation, angiogenesis and fibrosis plays a significant role in the disease pathogenesis. Fibroblast growth factor 2 (FGF2) is a vigorous mitogenic agent and a molecule associated with pathways that are effective in the pathogenesis of psoriasis. The purpose of this study is to determine the level of patients with FGF2 in the serum of psoriasis and to determine the change in the level of this molecule according to the severity of the disease.

Materials and Methods: 96 patients with psoriasis and 100 healthful were included in this study. The level of FGF2 was measured by ELISA method from serum samples obtained from blood samples taken from those included in the study. The results were compared with the healthful control group. Patients with psoriasis were grouped as mild, moderate, severe and very severe. FGF2 levels were compared in patients grouped according to disease severity.

Results: Serum FGF2 levels were found to be higher in psoriasis patients compared to the healthful control group ($p<0.0001$). When psoriasis patients were checked against the healthy control group according to the severity of the disease, serum FGF2 levels were found to increase in the moderate, severe and very severe patient groups ($p<0.001$).

Conclusion: Elevated serum FGF2 level in psoriasis patients was revealed for the first time. As the severity of the disease increases, the increase in the serum FGF2 level shows that this molecule may be effective in the pathogenesis of psoriasis and may be the target molecule in treatment.

Introduction

Psoriasis is a skin disease characterized by hyperproliferation and widespread chronic inflammation of the epidermis [1]. Since it affects people physically, emotionally and psychosocially, it has negative contributions to public health and health expenditures [1].

For this reason, it has been defined by the World Health Organization as a major global health problem. The severity, features, and prognosis of this disease differ between patients [2]. Psoriasis is an immune-mediated disease with a genetic predisposition, but no specific immunogen has been identified. It has been reported that cytokines, dendritic cells and T lymphocytes are effective in psoriatic lesions [3]. Although genetic predisposition is effective in the pathogenesis of this disease, infections act a significant role in the emergence and recurrence of the illness. The prevalence of psoriasis in adults ranges from 0.51% to 11.43%, and from 0 to 1.37% in children. Psoriasis occurs more frequently with advancing age [4]. Age, obesity, hypertension, diabetes, smoking and alcohol use are traditional risk factors. In addition, vascular endothelial damage, atherosclerosis, and inflammation have also been reported to be effective in the etiopathogenesis of the disease [1].

Fibroblast growth factor 2 (FGF2) is an important agent of the FGF family that stimulates cell division. FGF2 is a molecule mainly involved in cell proliferation, migration, and differentiation. In addition, it has been demonstrated to arrange many cellular missions, especially angiogenesis, in various tissues such as skin, muscle, blood vessel, tendon/ligament, adipose, tooth, bone, nerve and cartilage [5]. FGF2 has also been reported to stimulate inflammation indirectly, though not directly [6]. Studies have shown that basal FGF induces collagen production by stimulating skin fibroblasts [7]. In the experimental animal study

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of Shinozaki M, et al., the addition of exogenous FGF was shown to increase fibrosis [8].

Psoriasis is a mixed autoinflammatory and autoimmune skin characterized by infiltration of immune cells and hyperproliferation of keratinocytes [9]. FGF2 is a molecule involved in cell proliferation, cell migration, inflammation, and fibrosis [5, 6, 8]. Although there are studies suggesting that FGF2 is effective in the etiopathogenesis of psoriasis [10], this is limited. Therefore, determining the role of FGF2 in psoriasis patients will contribute to the elucidation of the pathogenesis of the disease and the identification of candidate molecules that can be used in treatment. The objective of this study is to determine the serum FGF2 in psoriasis patients and to reveal the relationship of this molecule with the severity of the disease.

Materials and Methods

This study was carried out on 94 patients with psoriasis and 100 healthy individuals followed in the S.B. Şanlıurfa Mehmet Akif Inan Training and Research Hospital as of January 2020. Ethics committee approval of this study was obtained from Harran University Clinical Research Ethics Committee in its meeting dated 30.12.2019 with decision number HRU.19.08.16. Anamnesis information such as sociodemographic characteristics, known diseases, history and family history characteristics, and medications used of all cases included in the study were recorded in a separate form. Whole blood collected in a flat tube without anticoagulant and gel was centrifuged at 4,000 rpm for 10 minutes, then separated into tubes and stored at -80 ° C.

Serum FGF2 [Human Fibroblast Growth Factor-2, (FGF2) ELISA Kit; MBS2020139; MyBioSource, USA] levels were measured by ELISA method in accordance with the instructions of the manufacturer.

The severity of patients with psoriasis was measured using the Psoriasis Area and Severity Index (PASI) score [11]. According to PASI, patients were disunited into four categories as mild psoriasis (n=11), moderate psoriasis (n=46), severe psoriasis (n=22) and very severe psoriasis (n=15).

Statistical analysis

The data provided from this study were analyzed with GraphPad Prism version 8.0.0 for Windows (GraphPad Software, San Diego, California, USA). Compliance of the numerical data with the normal distribution was tested with the Shaphiro-Wilk test. Mean±standard deviation (SD) values are given as descriptive statistics. The Mann-Whitney U test was used to compare the mean difference between two independent groups. Tukey's multiple comparison test was used to compare the variables in 3 groups. Results were considered significant at $p<0.05$ at the 95% confidence interval.

Results

A total of 194 people, including 94 patients with psoriasis (50 females and 44 males) and 100 healthy controls (52 women and 48 males), were included in the study. When the patient and control groups were compared in terms of age, body mass index (BMI), and sex, there was no significant differences between the groups (Table 1). Serum FGF2 levels were found to be significantly higher in patients with psoriasis compared to the control group. (Table 1 and Figure 1A).

Table 1. Age, BMI and serum FGF2 level in psoriasis patients and healthy controls.

	Psoriasis (n=94)	Control (n=100)	p
Age (years)	37.82±14.82	36.10±12.87	0.566
BMI (kg/m^2)	22.47±4.00	22.10±2.71	0.623
FGF2 (ng/mL)	27.0±9.62	17.17±6.84	<0.0001*

*Mann Whitney U test, BMI; Body mass index. Data are given as mean±standard deviation (SD).

Table 2. Age, BMI and serum FGF2 level in psoriasis patients grouped according to disease severity.

	Mild (n=11)	Moderate (n=46)	Severe (n=22)	Very Severe (n =15)	p*
Age (years)	60.66±6.65	37.46±15.62	31.08±11.34	41.50±7.91	<0.05
BMI (kg/m^2)	24.89±3.75	21.70±4.43	22.74±3.33	24.03±3.08	0.300
FGF2 (ng/mL)	20.58±8.66	25.48±8.97	27.50±8.97	35.63±7.75	**

*Dunnett's multiple comparisons test; **p value is given in Figure 1. Data are given as mean±standard deviation (SD).

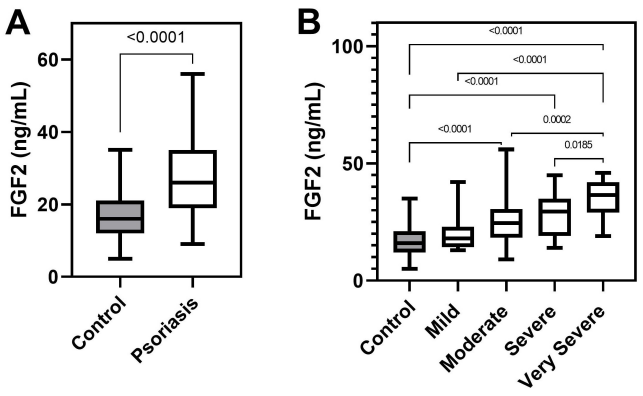

Figure 1. Comparison of FGF2 level. (A) Comparison of serum FGF2 levels in psoriasis patients and healthy individuals. (B) Comparison of FGF2 levels according to disease severity in psoriasis patients.

Patients with psoriasis were grouped according to PASI. FGF2 levels were found to be significantly higher in patients with mild, moderate, severe, and very severe psoriasis compared to the control group (Table 2 and Figure 1B). It was found that the FGF2 level of the patients grouped according to the disease severity was very severe when compared to mild, very severe compared with moderate, and very severe compared with severe poriasis patients had a significantly higher FGF2 level (Figure 1B).

Discussion

In addition to the limited number of studies carried out before, this study showed high serum FGF2 levels in pso-

riasis patients. In addition, it was first shown that the level of FGF2 increased as the severity of psoriasis disease increased.

Psoriasis is a multisystem inflammatory disease with predominantly skin and joint involvement [12]. This disease is characterized by hyperproliferation of keratinocytes and infiltration of immune cells [9]. Limited studies investigated the role of FGF2 in psoriasis. In this study, serum FGF2 levels were revealed for the first time to be high in psoriasis patients. FGF2 is a molecule involved in cell proliferation, migration, inflammation, and fibrosis pathways [5, 6, 8]. There are many studies that report that these pathways are associated with the pathogenesis of psoriasis [9]. Therefore, we believe that our findings are consistent. However, in this study, it was found that as the severity of the disease increased, the level of FGF2 increased. This supports the idea that FGF2 is an effective molecule in the pathogenesis of psoriasis.

The process of angiogenesis and the formation of new blood vessels is a critical stage for psoriasis [13]. FGF is an effective molecule in angiogenesis. Therefore, FGF-targeted treatment protocols are promising in diseases where angiogenesis is important (13). The role of inflammation in the pathophysiology of angiogenesis is becoming increasingly clear and shows that these two processes use common signaling pathways [14]. Molecules released during inflammatory reactions can produce pro-inflammatory cytokines with pro-angiogenic properties that promote the creation of new vascular structures [15]. Newly formed vascular structures maintain inflammation by facilitating the collection of inflammatory cells to the inflammation site [16]. This vicious cycle causes the disease to exacerbate and increases its severity. Considering these studies, it supports that the increase in FGF2 is significant in psoriasis as the disease severity increases. Although the role of FGF2 in this disease has not been fully revealed, the findings obtained in this study are believed to contribute to this issue.

On the other hand, perhaps the most remarkable finding obtained in this study is that although the serum FGF2 level in psoriasis increases as the severity of the disease increases, this phenomenon was not observed in patients with mild severity. This finding was interpreted as FGF2 was not effective in the onset of psoriasis, and the increase in FGF2 level could be the result of the disease. However, more clinical studies are needed to confirm this finding.

The hallmark of psoriasis is constant inflammation; this leads to uncontrolled proliferation and dysfunctional differentiation of keratinocytes [17]. Studies have shown that FGF application in wound healing stimulates keratinocyte migration [18]. In another study, in an animal model study in which lung damage was created, it was shown that FGF2 administration reduced inflammation by acting on the AKT/P38/NF-kB pathway [19]. From these studies, it was emphasized that keratinocyte proliferation is important in psoriasis, and the role of FGF2 in promoting keratinocyte migration. From this point of view, it is believed to support the findings obtained in this study. Experimental studies at the molecular level are required before making a final judgment on this issue.

The proliferation of various immune cells, inflammation, and angiogenesis play a role in the pathogenesis of psoriasis. Likewise, FGF2 has been reported to be effective in the same pathways. Therefore, revealing the relationship between psoriasis and FGF2 is important to elucidate the pathogenesis and determining new treatment approaches. As the severity of the disease increases, the increase in the level of FGF2 strengthens the idea that treatment protocols targeting this molecule may be effective. The number of patients included in this study was based on a larger number of patients compared to their peers. Since the centre where the study was conducted is a region with a high population rate, the number of patients with psoriasis is high. Therefore, the results are considered to be more reliable. First of all, the cause-effect relationship of FGF2 in psoriasis should be revealed by more advanced methods. As the disease severity increases, detection/confirmation of the increase in FGF2 level with more advanced methods may enable this molecule to be used as a new option in the treatment of psoriasis.

Ethical approval

Ethics committee approval of this study was obtained from Harran University Clinical Research Ethics Committee in its meeting dated 30.12.2019 with decision number HRU.19.08.16.

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