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Evaluation of the Diagnostic Significance of Some Biomarkers in Pruritic Dermatological Diseases: A Case-Control Study

Kaşıntılı Dermatolojik Hastalıklarda Bazı Biyobelirteçlerin Tanısal Öneminin Değerlendirilmesi: Bir Vaka Kontrol Çalışması

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ABSTRACT Objective: Indolamine-2,3-dioxygenase (IDO), neopterin, periostin, tenascin-C (TN-C), chitinase-3-like protein 1 (CHI3L1/YKL-40) YKL-40 have been previously described as diagnostic markers for a number of pathologies. The aim of our study is to compare the levels of some immune system-related biomarkers in itchy dermatological diseases with healthy people and to evaluate the diagnostic importance of these markers in dermatological diseases. **Material and Methods:** Our study included 55 patients diagnosed with neurodermatitis, generalised pruritus and lichen planus. The control group was composed of 30 healthy adult volunteers with no history of allergic skin conditions. All participants provided informed consent for the use of their medical data in the study. The serum samples were centrifuged. Centrifuged samples were stored at -80 ˚C. IDO, neopterin, periostin, TN-C, YKL-40 levels were determined by an enzyme-linked immunosorbent assay. The Mann-Whitney U test, Kruskal-Wallis test, and Conover post-hoc method were used for statistical analysis. **Results:** Demographic characteristics were recorded and no statistically significant difference was found between demographic differences. IDO, neopterin, periostin, TN-C, YKL-40 levels were higher in patients than in controls ($p<0.05$). The Th1/Th2-mediated immune response activation has been observed in allergic skin diseases. A positive correlation was found between all measured parameters ($p<0.01$). **Conclusion:** In our study, non-invasive current biomarkers that can be used in the diagnosis of dermatological pathologies yielded significant results. We found higher levels of serum biomarkers in patients compared to controls. It remains uncertain whether the examined protein is related only to inflammation or is released also as a result of specific biochemical processes due to allergy. However, these indicators may still have an important place in terms of early diagnosis.

Keywords: Indoleamine-2,3-dioxygenase; neopterin; periostin; pruritic diseases; tenascin-C

ÖZET Amaç: İndolamin-2,3-dioksijenaz (IDO), neopterin, periostin, tenascin-C (TN-C), kitinaz-3-benzeri protein 1 (CHI3L1/YKL-40), daha önce bir dizi patolojinin tanısal belirteçleri olarak tanımlanmıştı. Çalışmamızın amacı, kaşıntılı dermatolojik hastalıklarda immün sistem ilişkili bazı biyobelirteçlerin düzeylerini sağlıklılarla karşılaştırmak ve bu belirteçlerin dermatolojik hastalıklardaki tanısal önemini değerlendirmektir. **Gereç ve Yöntemler:** Çalışmamıza nörodermatit, jeneralize kaşıntı, liken planus tanısı almış 55 hasta dâhil edildi. Kontrol grubu, alerjik cilt rahatsızlığı öyküsü olmayan 30 sağlıklı yetişkin gönüllüden oluşturuldu. Tüm katılımcılardan, çalışmada tıbbi verilerinin kullanılması için bilgilendirilmiş onam alındı serum örnekleri santrifüjlendi. Santrifüjlenen örnekler -80 ˚C'de saklandı. IDO, neopterin, periostin, TN-C, YKL-40 seviyeleri, enzime bağlı immünosorbent deneyi ile belirlendi. İstatistiksel analiz için Mann-Whitney U testi, Kruskal-Wallis testi ve Conover "post hoc" yöntemi kullanıldı. **Bulgular:** Demografik özellikler kaydedildi ve demografik farklılıklar arasında istatistiksel olarak anlamlı bir fark bulunmadı. IDO, neopterin, periostin, TN-C YKL-40 seviyeleri hastalarda kontrole göre yüksekti ($p<0.05$). Alerjik cilt hastalıklarında Th1/Th2 aracılı immün yanıt aktivasyonu gözlenmiştir. Ölçülen tüm parametreler arasında pozitif yönde bir korelasyon bulundu ($p<0.01$). **Sonuç:** Çalışmamızda, dermatolojik patolojilerin tanısında kullanılabilen noninvaziv güncel biyobelirteçler önemli sonuçlar vermiştir. Kontrollere kıyasla hastalarda daha yüksek serum biyobelirteç seviyeleri bulduk. İncelenen proteinin yalnızca iltihaplanma ile ilişkili olup olmadığı veya aynı zamanda alerjiye bağlı spesifik biyokimyasal süreçlerin bir sonucu olarak da salgılanıp salgılanmadığı belirsizliğini korumaktadır. Ancak bu göstergeler, erken tanı açısından hâlâ önemli bir yere sahip olabilir.

Anahtar Kelimeler: İndolamin-2,3-dioksijenaz; neopterin; periostin; kaşıntılı hastalıklar; tenascin-C

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The skin is the largest organ in the human body with important immunological functions that make it a target for allergic and immunological responses. Both internal and external factors as well as innate and adaptive immunity responses act on the skin barrier. Several skin conditions, such as urticaria, atopic dermatitis (AD), angioedema, contact dermatitis, autoimmune bullous disease and psoriasis are immune-mediated, and are associated with underlying abnormalities in innate immunity. Most of these conditions involve proliferative and chronic inflammatory processes, in which both environmental and genetic agents play an important role.[1] The skin is vulnerable to external damage, autoimmunity and chronic inflammation, and tissue damage causes alterations in configuration and cell type in lesional skin. Programmed cell death, inflammation, immune disorders and tumorigenic, tumor proliferative and cytoreductive activities arouse a universal biological response called tissue remodeling. The need for a suitable environment facilitating tissue remodeling is coupled with changes in the extracellular matrix components.[2] Periostin, is one of the extracellular matrix (ECM) components. This glycoprotein, is secreted mainly by dermal fibroblasts. In normal skin, it is found primarily in the epidermal basement membrane and the papillary dermis, but a higher level of expression is observed in the dermis of the lesional skin of those with systemic scleroderma, AD, scars and cutaneous T-cell lymphoma, and an increased expression is observed in allergic/autoimmune responses. Periostin also leads to the development of dermal fibrosis, activating or prolonging the immune response.[3] Neopterin is synthesized from guanosine triphosphate by macrophages and monocytes activated by T-lymphocytes, and is synthesized and released into plasma by activated macrophages only in humans and primates.[4] Accordingly, elevated neopterin levels indicate the production of endogenous IFN-gamma, and their measurement allows the monitoring of the activation of the cell-mediated immune system. In short, neopterin concentration measurements not only serve as a laboratory diagnostic tool, but also enable the examination of the immunological network.[5] YKL-40, also known as chitinase-3-like protein 1, is a proinflammatory protein involved not only in immune process and inflammation. YKL-40 is also involved in the regulation of cell differentiation, proliferation and apoptosis.[6] Tenascin-C (TN-C) is an ECM protein found in several molecular forms. TN-C is expressed at high levels de novo in pathological conditions or during wound healing, including cancer and chronic inflammation.[7] In addition, the indolamine-2,3-dioxygenase (IDO) pathway has been found to substantially provide to the control of allergic inflammation, although it is better known for its immunomodulatory role in autoimmunity, pregnancy and infection.[8]

MATERIAL AND METHODS

STUDY POPULATION AND PROTOCOLS

The study group comprised 55 patients who presented to İnönü University Turgut Özal Medical Center Department of Dermatology and who were subsequently diagnosed with neurodermatitis, generalized pruritus and lichen planus (LP), while the control group comprised 30 individuals. Patients who were admitted to the hospital with itching complaints and diagnosed with itchy disease were included in the study. Those with secondary dermatological diseases other than pruritic diseases were excluded from the study. The location of the lesions, dermatological evaluation, duration of the disease, family history, and presence of secondary systemic disease were recorded in the patient group (Table 1). An approval was granted from the Inonu University Malatya Clinical Research Ethics Committee with decision number: 2020/03, date: 15.01.2020). All patients provided informed consent for the use of their medical data in the study, which was conducted in conformity with the principles of the Declaration of Helsinki. 1-2 ml peripheral venous blood was collected from all study participants in standard biochemistry tubes. After centrifuging the blood samples at 3,500 rpm for 15 minutes at room temperature, the sera were transferred into tubes after separation and stored at -80 °C until the time of analysis.

LABORATORY ANALYSIS

Serum concentrations of neopterin, YKL-40, periostin, TN-C and IDO were determined by the en-

zyme-linked immunosorbent assay technique using commercially available kits (Bioassay Technology Laboratory, BT Lab) in accordance with the manufacturer's instructions. The results were evaluated in nmol/L for neopterin, in ng/ml for YKL-40, periostin and IDO, and in ng/L for TN-C.

STATISTICAL ANALYSIS

The statistical analysis of the study findings was carried out using the SPSS (Statistical Package for Social Sciences) for Windows 11.5 software package. The relationships between the parameters measured in the study group were analyzed using Pearson/Spearman correlation tests. Calibration lines were prepared and calculated using a regression analysis, while a non-parametric Mann-Whitney U test was used to compare the means of the groups. An alpha of 0.05 was used to evaluate statistical significance.

RESULTS

The study included a total of 85 participants, with 30 (male/female: 9/21) in the control group and 55 (male/female: 29/26) in the study group. The mean age was 44.4±6.9 (minimum-maximum: 15-57) years and 48.1±14.3 (minimum-maximum: 17-79) years in the control and study groups, respectively. Age distribution in the study groups are shown in Figure 1. Table 1 displays general characteristics of the study patients; parameter measurements in the study groups are shown in Table 2; correlations between biomarkers are shown in Table 3.

DISCUSSION

Periostin is a biomolecule that has received considerable interest, having been the subject of several studies in recent years, and was shown to promote eosinophilic inflammation in the respiratory tract and other mucosal organs under the influence of Th2 cytokines.[9,10] As a fasciclin ECM protein, periostin functions upon binding to the cell surface receptors of the integrin family that includes αvß3 and αvß5. Upon stimulation by various stimulants, including Th2 cytokines, interleukin (IL-4), IL-13 and transforming growth factor ß, periostin is secreted by at least three types of cells, including endothelial cells,

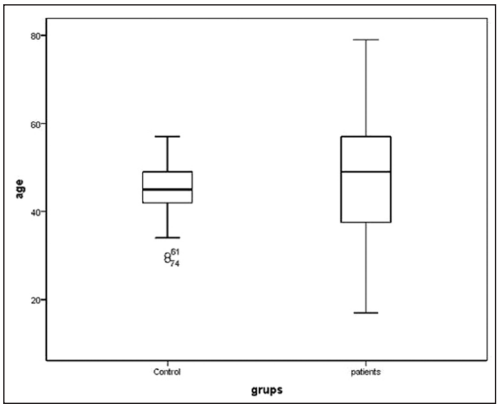

FIGURE 1: Age distribution in the study groups.

TABLE 1: The general characteristics of the patients.

	n	%
Diagnosis		
Neurodermatitis	19	35
Generalized pruritus	28	51
Lichen planus	8	14
Lesion involvement		
Body	24	44
Hand-feet	9	16
Arm	8	14
Leg	7	13
Head-neck	7	13
Dermatological examination		
Excoriation	17	31
Erythema	9	16
Brown patch	7	13
Hypo-hyperpigmentation	6	11
Xerosis	5	9
Dry itching	5	9
Natural	4	7
Creatotic papules	2	4
Duration of illness		
0-6 month	25	45
6-12 month	11	20
1-3 year	7	13
3-5 year	7	13
>5 year	5	9
Family history		
No	54	98
Yes	1	2
Secondary systemic disease		
No	33	60
Yes	22	40

TABLE 2: Parameter measurements in the study groups.

	YKL-40 (ng/mL)	Periostin (ng/mL)	Neopterin (nmol/L)	TN-C (ng/L)	IDO (ng/mL)
Control	13.4±4.8	4.7±2.3	4.0±4.8	1759±437	4.2±1.9
Patient	24.5±20.0	10.0±9.4	15.6±18.0	2751±2118	5.8±4.2
p value	**0.004**	**0.003**	**0.001**	**0.013**	**0.022**

YKL-40: Chitinase-3-like protein 1; TN-C: Tenascin-C; IDO: Indolamine-2,3-dioxygenase.

TABLE 3: Correlations between biomarkers.

		Periostin (ng/mL)	Neopterin (nmol/L)	TN-C (ng/L)	IDO (ng/mL)
YKL-40 (ng/mL)	rs	0.732**	0.402**	0.655**	0.703**
	p value	**0.000**	**0.000**	**0.000**	**0.000**
Periostin (ng/mL)	rs		0.547**	0.812**	0.926**
	p value		**0.000**	**0.000**	**0.000**
Neopterin (nmol/L)	rs			0.788**	0.521**
	p value			**0.000**	**0.000**
TN-C (ng/L)	rs				0.794**
	p value				**0.000**

**Correlation is significant at the 0.01 level (2-tailed); TN-C: Tenascin-C; IDO: Indolamine-2,3-dioxygenase; YKL-40: Chitinase-3-like protein 1.

epithelial cells and fibroblasts.[11] Periostin is expressed at high levels in the skin that is known to be rich in fibroblasts, and the strongest immunostaining is observed at the dermoepidermal junction. Periostin appears to be a critical player in terms of granulation and remodeling stages of cutaneous wound healing, as it is involved in the differentiation and migration of fibroblasts and the proliferation of keratinocytes. Periostin is also expressed in various diseases, such as pulmonary and systemic fibrosis hypertrophic scars, psoriasis and bronchial asthma, in which fibrosis is observed.[12]

The present study identified a significant difference in periostin levels between the study and control groups. Literature contains studies that have identified significantly increased serum levels of periostin in patients with AD, as in the present study.[10,13] Periostin has specific effects on AD pathogenesis involving the release of proinflammatory cytokines and chemokines from activated keratinocytes.[14,15] In a previous study involving in vitro organotypic culture systems, it was found that periostin promoted the survival and proliferation of keratinocytes and the production of directly induced thymic stromal lymphopoietin (TSLP). Based on these findings, the authors suggested that periostin aggravates AD pathogenesis through TSLP production from keratinocytes.[10] As in AD, significant results have also been demonstrated in systemic sclerosis. A previous study involving patients with systemic sclerosis reported a correlation between high levels of periostin and the severity of skin sclerosis, and it was suggested that periostin could be used as a potential biomarker for the assessment of disease severity in systemic sclerosis.[16] Periostin levels were found to be correlated with the severity of itching in patients with bullous pemphigoid. While the direct or indirect effects of periostin and basophils on itching are unclear, it is believed that they are involved in the pathogenesis of bullous pemphigoid.[17] Likewise, the cause of periostin overexpression in scabies is unknown, although it may be connected with the production of the Th2-associated cytokines IL-4/13, which promotes periostin secretion.[18] A vast majority of studies investigating the role of periostin in dermatological disease focus on AD and pruritus, while no study could be identified investigating neurodermatitis which is evaluated in the present study.

TN-C was found to instigate the synthesis of proinflammatory cytokines, and has been reported to be associated with both proinflammatory and antiinflammatory signaling cascades.[19] In the study by

Ogawa et al., it was suggested that the upregulation of TN-C expression is specific to the AD lesions, and that TN-C may therefore be involved critically in the regulation of inflammatory processes underlying the AD pathology. Although the molecular details of TN-C function in AD skin lesions are not fully known, TN-C is believed to have an important role in the regulation of the inflammation underlying AD.[20] The increased expression of TN-C and other remodeling markers was identified in all acute eczematous lesions of patients with allergic and irritant contact dermatitis.[21] Aside from these studies, there have also been studies establishing no significant results regarding TN-C. In a study measuring the serum TN-C levels in psoriasis and a control group, it was found that the TN-C levels of most of the patients were within the normal range, and that TN-C values were not correlated with disease activity. The authors concluded that TN-C could not be used as a marker for disease activity in psoriasis.[22] The present study found TN-C levels to be high in the study group. A review of literature revealed no previous study evaluating the relationship between TN-C, and neurodermatitis and seborrheic dermatitis, while in an animal study in which chronic contact dermatitis was induced, an apparent increase was noted in fibronectin and TN-C levels, and a considerable accumulation of TN-C in the connective tissue in the acute phase (day 3-day 12) of the inflammation. TN-C was observed mainly on and below the epidermal basement membrane.[23]

The tryptophan-consuming enzyme IDO is of vital importance in the regulation of immunotolerance, and plays a significant role in immune-associated skin disorders, although an increase in IDO may not be sufficient to mediate immunotolerance-related skin disorders.[24] IDO protein is locally increased in vitiligo, while the enzymatic activity for the tryptophan metabolism shows a state of inactivation.[25] Furthermore, the over-expression of IDO may be involved in protective antiinflammatory response in certain type I mediated skin disorders, including LP, psoriasis and chronic discoid lupus erythematosus.[26] In a previous study evaluating a number of common childhood allergic diseases, such as AD, allergic rhinitis and asthma, the most remarkable IDO-1 activity was observed in patients with AD among the patient groups.[5] IDO also produced significant results in studies of AD in adults, and is one of the few biomarkers with parallel upregulation in the blood and skin in AD in this population. IDO thus serves as an immune checkpoint molecule.[27] A review of literature on the role of IDO in dermatological diseases identified no study relating to neurodermatitis and seborrheic dermatitis. In a previous study of contact dermatitis, IDO was assessed through tryptophan catabolism, with no direct measurement made of IDO activity.[28]

The role of YKL-40 has been determined in a number of dermatological pathologies, such as AD, psoriasis, Behçet's disease, hidradenitis suppurativa and LP.[29-31] The apparent elevation in YKL-40 levels in patients with LP can be explained through systemic and local YKL-40 expression in different cell types. YKL-40 is secreted by natural killer cells, monocyte-macrophages, endothelial cells T and B, lymphocytes, fibroblasts, Langerhans cells, mast cells, and keratinocytes. It is thus likely to play a role not only in the local but also systemic immunopathogenesis of LP, which is an immune-related disorder.[6] Previous studies support its pathogenic role in LP. Although it is expressed and secreted by inflammatory cells, such as fibroblasts neutrophils, chondrocytes macrophages, smooth muscle cells and endothelial cells, the uncertainty persists regarding its biological role.[6,32] That said, studies have suggested that YKL-40 is incorporated into both adaptive and innate type 2 immunity, and takes part in cell proliferation, inflammation, tissue remodeling and angiogenesis.[32] In addition to the role of YKL-40 in the AD pathology, it was found also that the serum level of YKL-40 is increased in AD patients, and that its concentration is reflected in the severity of skin diseases. Moreover, it has also been associated with pruritus, as the most significant and main subjective symptom of AD. The cause of elevated YKL-40 levels is obscure; however, it might be accepted that this protein is released by the inflammatory cells that become activated during the disease. Recent studies have shown how YKL-40 contributes to type 2 allergic response mechanisms and have determined the relationship of such mechanisms with atopy.[31]

CONCLUSION

These results indicate that serum IDO, neopterin, periostin, TN-C, YKL-40 levels may be used as a reliable immunological marker for monitoring the dermatologic pathologies. The study has found an elevated serum level of biomarkers; however, there is a lack of knowledge regarding the exact mechanisms underlying such an elevation. The study is limited by some aspects; the examined group of patients has been rather small. The above described findings may comprise another proof for the role of IDO, neopterin, periostin, TN-C, YKL-40 in pruritic dermatologic diseases but it actually requires further investigations.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Songül Ünüvar, Dursun Türkmen;* ***Design:*** *Songül Ünüvar, Neşe Başak Tükmen;* ***Control/Supervision:*** *Songül Ünüvar, Hande Yüce, Zübeyde Tanrıverdi;* ***Data Collection and/or Processing:*** *Mücahit Marsak, Hande Yüce;* ***Analysis and/or Interpretation:*** *Songül Ünüvar, Zübeyde Tanrıverdi;* ***Literature Review:*** *Songül Ünüvar, Hande Yüce, Zübeyde Tanrıverdi;* ***Writing the Article:*** *Songül Ünüvar;* ***Critical Review:*** *Songül Ünüvar, Neşe Başak Tükmen;* ***References and Fundings:*** *Dursun Türkmen, Mücahit Marsak;* ***Materials:*** *Mücahit Marsak, Dursun Türkmen.*

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