DOI: http://doi.org/10.32792/utq.jceps.10.01.01

Assessment of IL-17 and IL-4 serum levels and their relationship to psoriasis pateints

Salah Mahdi Muttar[1] , Dr. Hassan RisanMubarek [2]and Dr. Ahmed AbdulhusseinKawin [3]

mailto:Salahmahdy-mo21.bio@utq.edu.iq, mailto:hassanresan.bio@utq.edu.iq, mailto:ahmed.abd.kh@utq.edu.iq

[1] General directorate of Education in Thi-Qar province, Ministry of Education / Iraq.
[2] Department of Biology / College of Education for Pure Sciences / University of Thi-Qar / Iraq.
[3] Department of Dermatology/ College of Medicine / University of Thi-Qar / Iraq.

Received 4/6/2023, Accepted 25/6/2023, Published 21/9/2023

Abstract:

Psoriasis is an immune-mediated disease (a disease with an unclear cause that is characterized by inflammation caused by dysfunction of the immune system) that causes inflammation in the body.This study included 100 patients and 50 healthy.Aquestionnaire was included sex and age of psoriatic patients and healthy subjects, also, psoriatic patients were distributed according to the period of infection, family history, severity of psoriasis, and comorbidities of psoriasis. Enzyme-linked immunosorbent assay (ELISA) used to measure the concentration levels of cytokines interleukin-17 (IL-17) and interleukin-4(IL-4) in the serum of the studied samples from both groups. The present results showed no significant differences between psoriatic patients and healthy subjects according to age(P=0.247) andsex (P=0.643), while asignificant differences was observed betweenpsoriatic patients inperiod of infection (P=0.000), family history (P=0.001), severity of psoriasis (P=0.000) and comorbidities of psoriasis (P=0.000), as well, the current results indicated an increase in the concentration level of IL-17 in psoriatic patients (150.61±55.7 pg/mL) compared with its concentration levels in healthy individuals (96.55±34.pg/mL), with significant difference (P=0.00) at (P≤0.05). Adecrease in the concentration levels of IL-4 in psoriatic patients (136.8±51.9 pg/mL) was observed in this study compared with its concentration levels in healthy individuals (193.84±69.10 pg/mL) with a significant difference between the two groups (P=0.002). It can be concluded that there is an immunologic imbalance of T cells in psoriasis, which is associated with the upregulation of IL-17 and the downregulation of IL-4 in the circulation. This immune dysregulation, which plays a key role in the disease progression.

Keywords:psoriasis, interleukin-17, interleukin-4, immune pathway, Thi-Qar Province patients.

1-Introduction

Psoriasis is a chronic, immune-mediated inflammatory condition that has a considerable effect on lifestyle **(1,2).**Psoriasis is distinguished by the presence of erythematous plaques with silvery-white scales that covering different parts of the body, particularly the scalp, elbows, knees and lower back.The appearance of scales is associated by itching, burning and tingling in some situation.It is a chronic disease that causes pain, so there is no whole cure for it, however there are numerous treatments used to reduce symptoms of disease **(3).** Reports exhibit that the incidence of psoriasis ranges between 2-3% in the world **(4).** Both males and females are influenced equally and the disease may be appear at any age group **(5,6).**Although, the causes of psoriasis is not completely known, however, there are some factors that may be involved in emergence of psoriasis, comprising: genetic, environmental, and autoimmune factors **(7).**

Genome-wide association studies have recognized more than 50 genetic loci linked with psoriasis risks **(8).**Psoriasis develops when activated plasmacytoid dendritic cells (pDC) produce the inflammatory cytokine Interferon-alpha (IFN-α), which activates myeloid dendritic cells (mDC), which in turn activate T helper 1 (Th1) and T helper 17 (Th17) cells. Once initiated, this cycle of inflammation continues simultaneously, with activated Th1 cells producing tumor necrosis factor-alpha (TNF-α) and Th17 cells producinginterleukin-17A (IL-17A) and interleukin-17F (IL-17F).These cytokines activate keratinocytes (KCs), which produce a variety of cytokines, chemokines, and antimicrobial peptides (AMP).This inflammatory pathway causes in immoderate proliferation of KC cells in the epidermis and in the lining of blood vessels, leading to hypertrophy of epidermis and the development of psoriasis**(9,10).**

Interleukin-17 (IL-17) is a pro-inflammatory cytokine that supportsconsistence of T-cells and activate epithelial, endothelial and fibroblastic cells for producing many pro-inflammatory mediators.IL-17 has been found to be linked with the pathogenesis of a wide range of inflammatory and autoimmune diseases, as well, IL-17 plays important role in coordinating autoimmune tissue inflammation.Inflammation induced by IL-17 is usually controlled by regulatory T cells and anti-inflammatory cytokines, for instance, IL-4 is a multifunctional cytokine that can be utilized guardedly and efficiently to correct abnormalities in immune function without posing risks of severe immunosuppression **(11).**In addition to the strong ability of IL-4 to regulate immunity, its main biological function is to reduce and terminate inflammatory responses. Therefore, it is considered an important cytokine for tissue repair as it balances the effects of pro-inflammatory type I cytokines and inhibits the expression of IL-17 and IL-23 in T cells and dendritic DC respectively **(12)**.The present study aims to determine the effect of serum levels of the cytokines IL-17 and IL-4 and their relationship to psoriasis in Thi-Qar province**.**

2-Materials and Methods

A- Samples Collection

One hundred fifty venous blood samples were collected in this study divided into 100 blood samples from psoriatic patients in Al-Nahrain laboratory for pathological analysis in Thi-Qar province after

the disease was clinically diagnosed by a dermatologist. also, 50 blood samples were collected from healthy individuals in gel tubes for the period from the beginning of March 2022 until June of the same year. The ages of those included in this study ranged between (5-70) years. Demographic and clinical data about psoriatic patients and healthy individuals including sex, age, period of infection, family history, severity of psoriasis, and comorbidities of psoriasis were organized in a questionnaire.

B- Determination of the concentration of cytokines IL-4 and IL-17 using an ELISA assay

– Isolation of serum from studied samples

Three milliliters of venous blood was placed in gel tubes (free of anticoagulant) and centrifuged at a speed of 2000-3000 rpm for 20 minutes for isolating the serum from samples of psoriatic patients and healthy individuals included in this study**(13)**.

– Measurement of cytokines levels

Cytokine levels (IL-17 and IL-4) were quantified using the (Sandwich ELISA assay) according to the instructions provided with the human IL-17 ELISA kit and the human IL-4 ELISA kit Manufactured by Shanghai Company.

Statistical Analysis

Standard statistical tests were used to analyze data. the chi-square test was used test to determine the significant differences between study groups at significant level $P \leq 0.05$. Data were analyzed with statistical package for the social sciences (SPSS) program (version 20)**(14)**.

3-Results

Distribution of psoriatic patients and healthy individuals according to age groups

Table (1) shows no significant differences between psoriatic patients and healthy individuals according to age (P=0.247), It was also noted when comparing patients that the highest rate of the disease was (31%) in
the age group (5-19) year, then it decreased to (14%) in the age group (50 years and over).

Table(1) Distribution of psoriatic patients and healthy individuals according to age groups.

Age groups	psoriatic patients		healthy individuals		P.value
	N	%	N	%	
5-19	31	31%	10	20%	0.247
20-34	29	29%	20	40%	
35-49	26	26%	16	32%	
50 year and over	14	14%	4	8%	
Total	100	100%	50	100%	

0.05≥P.value4.13 df=3=X^2

Distribution of psoriatic patients and healthy individuals according to Sex.

The present study showed that the percentage of male in patients (52 %) and healthy (56%) when compared with females (48%) and (44%) in patients and healthy respectively. Results of statistical analysis demonstrate no significant differences between two groups according to sex (P=0.643). Table (2).

Table(2) Distribution of psoriatic patients and healthy individuals according to Sex.

Age groups	psoriatic patients		healthy individuals		P.value
	N	%	N	%	
Males	52	52%	28	56%	0.643
Females	48	48%	22	44%	
Total	100	100 %	50	100%	
0.05≥P.value0.21 df=1=X^2					

Distribution of psoriatic patients according to period of infection.

The present results indicated that (67%) of psoriaticpatients had period of infection from (1-15) years, whereas (6%) of them ranged from (16-30) year, and (27%) of patients was less than one year. Results of statistical analysis showed high significant differences between patients group according to period of infection (P=0.000). Table (3).

Table (3) Distribution of psoriatic patients according to period of infection.

Duration of infection (Year)	psoriatic patients		P.value
	N	%	
Less than one year	27	27%	0.000
1-15	67	67%	

16-30	6	6%	
Total	100	100%	
0.05≥P.value57	df=2=X^2		

Distribution of psoriatic patients according to family history.

Table (4) exhibit that (72%) of the psoriatic patients had no family history, where, (28%) of them were found to have a family history of the disease. Statistical analysis showed significant difference between patients group according to family history of disease (P=0.001).

Table (4) Distribution of psoriatic patients according to family historyof the disease.

Family history	Psoriatic patients		P.value
	N	%	
Present	28	28%	0.001
Absent	72	72%	
Total	100	100%	
0.05≥P.value23.51	df=1=X^2		

Distribution of psoriatic patients according toseverity of psoriasis.

Table (5) indicated distribution of patients according to severity of psoriasis to mild, moderate and severe. Rate of infection with mild psoriasis was (53%) while rate of infection moderate psoriasis (37%) and severe psoriasis (10%). Significant difference was observed according to severity of psoriasis (P=0.000).

Table (5) Distribution of psoriatic patients according to severity of psoriasis.

severity of psoriasis	Psoriatic patients		P.value
	N	%	
Mild	53	53%	0.000
Moderate	37	37%	
Severe	10	10%	
Total	100	100%	
0.05≥P.value28.34 df=2=X^2			

Distribution of patients according to Comorbidities of psoriasis.

The present study showed that (87%) of patient had no Comorbidities of psoriasis whereas (13%) of them suffering from diseases associated with psoriasis. Statistical analysis showed significant difference between patients group according to Comorbidities of psoriasis (P=0.001).Table (6).

Table (6) Distribution of psoriatic patients according to comorbidities of psoriasis.

Comorbidities of psoriasis	psoriatic patients		P.value
	N	%	
Arthritis	5	5%	0.000
Heart diseases	2	2%	
Diabetes	3	3%	
Kidney infection	3	3%	
No disease	87	87%	
Total	100	100%	
P.value≥ 0.05			

Level of cytokinesis IL-17 in patients and healthy groups

A significant increase in the concentration of IL-17 in serum ofpsoriatic patients was observed in this study (150.61±55.7pg/mL) when compared to its concentration in serum of healthyindividuals (96.55±34.2pg/mL). Statistical analysis demonstrate there is significant differencein the concentration of IL-17between patients and healthy groups (P=0.00*).Table(7).

Table (7) Level of cytokinesis IL-17concentration in patients and healthy groups.

Level of cytokinesis	Patients group N=100	Healthy group N=50	T.value	P.value
IL-17	150.61±55.7	96.55±34.2	4.50	0.00*
df=148				

Level of cytokinesis IL-4 in patients and healthy groups

Table (8) shows a decrease in the concentration of IL-4 in patients serum (136.8±51.9pg/mL) compared to its concentration in healthy serum (193.84±69.10pg/mL). Results of the statistical analysis showed a significant difference in the concentration of IL-4 between patients and healthy groups (P=0.002*).

Table (8) Level of cytokinesis IL-4concentration in patients and healthy groups

Level of cytokinesis	Patients group N=100	Healthy group N=50	T.value	P.value
IL-4	136.8±51.9	193.84±69.10	-3.29	0.002*
df=148				

Discussion

Psoriasis can happen at any age group, as some studies showed that a third of psoriasis cases begin in childhood **(15).** Whereas, other studies mentioned that the average age of onset of psoriasis was 33 years and that 75% of cases occurred before 46 years **(16).** The present study indicated that there was no significant difference between the patients and healthy groups according to age. It was also noted when comparing patients that the highest rate of disease was (31%) within the age group (5-19) years, then it decreased to (14%) in the age group (50 years and over).Similarly, a study by**(17)** showed that the highest rate of psoriasis was (48%) in age group (less than 20 year) whereas, the lowest rate was (5%) in the age group over 40 years. This is probably because Patients with an early onset of psoriasis seem to have more severe disease and a more frequent family history**(18)**. Also, a

study conducted by**(19)** showed a significant decrease in serum levels of IL-17 with increasing age.In contrast, the study of **(20)** in Denmark the highest rates of psoriasis were reported among individuals aged 60-69 years and the lowest among individuals aged (1-19) years. This may be due to age-related changes that contribute to increased susceptibility to pharmacodynamics or to skin changes that make the skin drier and reduce its resistance to environmental influences and its ability to regenerate. **(21)**.

Although, the prevalence of psoriasis was equal in both sex **(16).**However, the present study recorded a higher prevalence of psoriasis in males (52%) when compared to females (48%). It was also noted that there was no significant difference between the patients and healthy individuals according to sex. The current results agreed with results of **(19)** who showed the higher prevalence of psoriasis in males (20%) and lower in females (10%) with no significant difference between two groups.However, it is unclear whether men are indeed more vulnerable to psoriasis, or if this finding comes from the difference in health-related behaviors between the sexes. To confirm this, further community-based study is necessary On the other hand, other studies showed the higher prevalence of psoriasis in females compared to males in Sweden (0.5 vs. 0.1) **(22)** and in Germany (0.76 vs. 0.66)**(23).** This may be due to the fact that male patients are generally more satisfied with psoriasis treatment, and that they respond better to biological therapies, despite often suffering from more serious disease. On the contrary, it seems that women usually experience a greater psychological impact and a lower quality than men. Furthermore, Previous data referred that sex hormones show a variety of biological and immunological characteristics that effects on the skin, pregnancy, menstruation, and menopause change natural course of psoriasis, which indicates the regulation of the skin inflammation can be induced by female hormones **(24)**.

The present study indicated that (67%) of patients had a duration of infection from (1-15) years, and (6%) of them ranged from (16-30 years), whereas (27%) of patients had a duration of infection of less than a year, this finding is in-agreement with the findings of a study in India by **(25)** that included 250 psoriatic patients, and showed that the incidence rate in patients with a duration of infection of less than 5 years was (62%), with an average duration of (6.53±6.7) and (3.26 ±3.58) years in the case of early-onset psoriasis and late-onset psoriasis, respectively. While a study conducted by **(26)** that included 118 patients with psoriasisrevealed that the highest prevalence was (64%) in patients whose duration of infection was more than 20 years and (55%) of patients had a duration of infection of less than 20 years.

A positive family history of psoriasis has been considered a risk factor for the development of the disease. In this study, (28%) of patients reported is having a family history of psoriasis in one or more members of their families . This emphasizes the important role of genetics as a causes of psoriasis, which is similar to previous reports (**27**). However, higher percentages have been reported in, Italy, Chile and Sweden **(28,29,30)**due to genetic background differences or combined data from more than one relative affected and/or the addition of affected second and third-degree relatives.

In the present study, the incidence of mild psoriasis was the most common (53%), while the lowest incidence noted in severe psoriasis (10%), with a very high significant difference.The present results agreed with results of **(31)** who reported that mild psoriasis was the most common (79%) inpsoriatic patients, and (17%) of them were suffering from moderate psoriasis, while (4%) suffering

from severe psoriasis. In contrast**, (32)** showed in a study conducted in India that comprised 100 psoriatic patients that (3%) of patients had mild psoriasis, and (55%) of them had moderate psoriasis, whereas (42%) had severe psoriasis. Differences in the clinical severity of psoriasis among patients can be explained by a combination of factors such as genetic and environmental factors, the type of psoriasis, the extent to which the skin is affected, the psychological state, the presence or absence of comorbidities of psoriasis, and the location of skin lesions such as: scalp, face, nails and ethnic area. **(33).**

The current study revealed that the percentage of psoriasis patients with who had systemic comorbidities of psoriasis was (13%), which is similar to the results of the study of **(34)** in Turkey who showed that (12%) patients with psoriasis had non-alcoholic fatty liver disease (NAFLD), which is a systemic comorbidity of psoriasis, is the most common liver disease in population with risk of cirrhosis progression. The systemic comorbidities are thought to be due to chronic inflammatory changes and elevated inflammatory cytokines present in psoriasis e.g. IL-17, IL-23 and TNF-α can reach anywhere in the body through the circulation and can mediate systemic inflammatory responses in psoriasis **(35)**. In contrast, a study conducted by **(36)** did not show any relationship between psoriasis and its comorbidities diseases (such as heart, metabolic syndrome and vascular diseases).

The present results revealed high levels of IL-17 in psoriatic patients serum (150.61±55.7pg/mL) compared to its levels in healthy blood serum (96.55±34.2pg/mL), with significant differences in the concentration of IL-17 between the patients and healthy groups.This result is consistent with a study**(37)**that showed significant differences in the level of IL-17 concentration in psoriatic patients (20.88 ± 0.31 pg/mL) and healthy individuals (13.12 ± 0.88 pg/mL). Another study (19) that revealed an increase in inserum levels of IL-17 in psoriatic patients (6.24±4.65pg/mL) with a significant difference when compared to healthy individuals (2.0± 0.75pg/mL).Similarly it was observed that the severity of psoriasis was associated with higher levels of IL-17 compared to patients with mild or moderate severity with a statistically significant difference ($p \leq 0.01$)**(38)**. These results suggest that IL-17 have a pro-inflammatory role in the pathogenesis of psoriasis and the increase in serum levels of IL-17 in patients with psoriasis could be due to an immunologic imbalance in T cells caused by genetic and environmental factors.In contrast, a study conducted by **(39)** showed no significant differences between psoriatic patients and healthy individuals, although the serum IL-17 concentration in patients was (4.24 ± 3.69 pg/mL) was higher than its concentration in the healthy individuals (3.06 ± 1.19 pg/mL).Also, other studies did not notice any significant difference in serum levels of interleukin-17 between patients with psoriasis and healthy individuals **(40,41)**. The differences among the results of above mentioned studies may be due to the variation in severity and duration of psoriasis and genetic difference between races, in addition to different ecological factors.

The present results showed a significant decrease in the concentration of IL-4 in psoriatic patients serum (136.8 ± 51.9 pg/mL) compared to its concentration in healthy blood serum (193.84 ± 69.10 pg/mL). This study agrees with a previous study by **(42)** showed a significant decrease in the concentration of IL-4 in serum level of psoriatic patients compared to healthy individuals**.** A study by **(12)** showed that IL-4 is strongly genetically linked to the development of psoriasis and that its expression is almost absent in the serum of psoriatic patients.IL-4 is involved in Th2 cell

differentiation which constitutes apotent positive reaction during T cell differentiation, Therefore, IL-4 can drive the cytokine environment towards a Th2-cell-dominated immune response **(43,44)**, possibly through impairment of Th17 function after decreased IL-23 production in antigen presenting cells (APCs) **(45)** or through induction of the transcription factor GATA3 **(46)** and other mechanisms**.**The decreased serum level of IL-4 in psoriasis patients could be caused by an immunologic imbalance of T cells in psoriasis, associated with downregulation of Th2 cytokines in circulation, as well as at the level of gene expression of their respective cytokines. In contrast **(47)** noted that levels of IL-4 was higher in patients (4.7 ± 1.91 pg/mL) compared with healthy group (0.3 ± 0.9 pg/mL), also, a study conducted by**(48)** did not show a significant difference between psoriatic patients and healthy individuals in serum IL-4 level, while, a study**(49**) noted that the serum IL-4 level was higher in patients with severe psoriasis compared with healthy group and patients with moderate psoriasis, whereas,a study **(50)** did not record any altration between psoriatic patients and healthy individuals in serum levels of IL-4.

References

1- Puig, L.; Thom, H.; Mollon, P.; Tian, H & Ramakrishna, G. S. (2017). Clear or almost clear skin improves the quality of life in patients with moderate-to-severe psoriasis: a systematic review and meta-analysis. Journal of the European Academy of Dermatology and Venereology, 31(2): 213-220.

2- Armstrong, A. W & Read, C. (2020). Pathophysiology, clinical presentation, and treatment of psoriasis: a review. Jama, 323(19): 1945-1960.

3- Nair, P. A &Badri, T. (2022). Psoriasis. University of Tunis El Manar**.**

4-Sewerin, P.; Brinks, R.; Schneider, M.; Haase, I.; &Vordenbaumen, S. (2019). Prevalence and incidence of psoriasis and psoriatic arthritis. Annals of the Rheumatic Diseases, 78(2): 286-287.

5- Jain, S. (2017). Dermatology: illustrated study guide and comprehensive board review.Generaldermatoiogy. 96-185.

6- Woo, Y. R.; Park, C. J.; Kang, H & Kim, J. E. (2020). The risk of systemic diseases in those with psoriasis and psoriatic arthritis: from mechanisms to clinic. International Journal of Molecular Sciences, 21(19): 7041**.**

7- Carvalho, A. L &Hedrich, C. M. (2021). The molecular pathophysiology of psoriatic arthritis—the complex interplay between genetic predisposition, epigenetics factors, and the microbiome. Frontiers in molecular biosciences, 8, 662-847.

8- Puscas, A. D.; Catana, A.; Puşcaş, C.; Roman, I. I.; Vornicescu, C.; Şomlea, M &Orasan, R. I. (2019). Psoriasis: Association of interleukin-17 gene polymorphisms with severity and response to treatment. Experimental and Therapeutic Medicine, 18(2): 875-880.

9- Dopytalska, K.; Ciechanowicz, P.; Wiszniewski, K.; Szymańska, E &Walecka, I. (2021). The role of epigenetic factors in psoriasis. International Journal of Molecular Sciences, 22(17): 9294.

10- Tashiro, T & Sawada, Y. (2022). Psoriasis and Systemic Inflammatory Disorders. International Journal of Molecular Sciences, 23(8): 4457.

11- Mills, K. H. (2022). IL-17 and IL-17-producing cells in protection versus pathology. Nature Reviews Immunology, 1-17.

12- Hahn, M &Ghoreschi, K. (2017). The role of IL-4 in psoriasis. Expert Review of Clinical Immunology, 13(3): 171-173.

13- Alghonemy, S. M. E., Obaid, Z. M., Elbendary, A. S., &Fouda, I. (2020). Assessment of serum elafin as a possible inflammatory marker in psoriasis. *Al-AzharAssiut Medical Journal*, *18*(4), 408-412.

14- Schefler, W.C. (1980). statstic for the biology science. Addison, Wesley publication company California.

15- Diotallevi, F.; Simonetti, O.; Rizzetto, G.; Molinelli, E.; Radi, G &Offidani, A. (2022). Biological Treatments for Pediatric Psoriasis: State of the Art and Future Perspectives. International Journal of Molecular Sciences, 23(19): 11128.

16- Guillet, C.; Seeli, C.; Nina, M.; Maul, L. V & Maul, J. T. (2022). The impact of gender and sex in psoriasis: What to be aware of when treating women with psoriasis. International Journal of Women's Dermatology, 8(2): 1-10**.**

17- Jankowiak, B.; Sekmistrz, S.; Kowalewska, B.; Niczyporuk, W &Krajewska-Kułak, E. (2013). Satisfaction with life in a group of psoriasis patients. Advances in Dermatology and Allergology/PostępyDermatologii i Alergologii, 30(2): 85-90.

18- Sanclemente, G., Mora, O., Velez, N., Diaz, C. J., Quevedo, E., Amador, J., &Charry, L. (2022). Epidemiologic characteristics and burden of psoriasis: A multicenter, cross-sectional study. Medwave, 22(8), 2564-2564.

19- Sobhan, M.; Basir, H. R. G.; Rabiee, M. A. S &Shadfar, F. (2022). Serum level of interleukin-17 in patients with psoriasis. ImmunopathologiaPersa,7(11), 946-952.

20- Egeberg, A., Skov, L., Gislason, G. H., Thyssen, J. P., &Mallbris, L. (2017). Incidence and prevalence of psoriasis in Denmark. Actadermato-venereologica, 97(7), 808-812.

21- Petersen, J., Garbe, C., Wolf, S., Stephan, B., Augustin, M., &Hagenström, K. (2022). Medicinal Treatment of Elderly Psoriasis Patients before and after Entering a Nursing Home. In Healthcare (Vol. 10, No. 9, p. 1730).

22- Larsson, P. A &Liden, S. (1980). Prevalence of skin diseases among adolescents 12--16 years of age. Actadermato-venereologica, 60(5): 415-423.

23- Augustin, M.; Glaeske, G.; Radtke, M. A.; Christophers, E.; Reich, K &Schäfer, I. (2010). Epidemiology and comorbidity of psoriasis in children. British Journal of Dermatology, 162(3): 633-636.

24- Murase, J. E., Chan, K. K., Garite, T. J., Cooper, D. M., & Weinstein, G. D. (2005). Hormonal effect on psoriasis in pregnancy and post partum. Archives of dermatology, 141(5), 601-606.

25- Fatema, F.; Ghoshal, L.; Saha, A.; Agarwal, S &Bandyopadhyay, D. (2021). Early-Onset versus late-onset psoriasis: A Comparative Study of Clinical Variables, Comorbidities, and Association with HLA CW6 in a tertiary care center. Indian Journal of Dermatology, 66(6): 705.

26- Driessen, R. J. B.; Boezeman, J. B.; Van de Kerkhof, P. C. M & De Jong, E. M. G. J. (2009). Three-year registry data on biological treatment for psoriasis: the influence of patient characteristics on treatment outcome. British Journal of Dermatology, 160(3): 670-675.

27- Solmaz, D.; Bakirci, S.; Kimyon, G.; Gunal, E. K.; Dogru, A.; Bayindir, O &Aydin, S. Z. (2020). Impact of having family history of psoriasis or psoriatic arthritis on psoriatic disease. Arthritis care & research, 72(1): 63-68.

28- Altobelli, E., Petrocelli, R., Marziliano, C., Fargnoli, M. C., Maccarone, M., Chimenti, S., &Peris, K. (2007). Family history of psoriasis and age at disease onset in Italian patients with psoriasis. British Journal of Dermatology, 156(6), 1400-1401.

29- Valenzuela, F., Silva, P., Valdés, M. P., & Papp, K. (2011). Epidemiology and quality of life of patients with psoriasis in Chile. ActasDermo-Sifiliográficas (English Edition), 102(10), 810-816.

30- Agerberg, K &Ronnblom, A. (2022). Debut of Psoriasis is usually before Debut of Concomitant Inflammatory Bowel Disease: A Population-based Retrospective Study. ActaDermato-Venereologica.

31- Tajalli, M.; Li, T.; Drucker, A. M.; Qureshi, A. A & Cho, E. (2021). A description of treatment patterns of psoriasis by medical providers and disease severity in US women. Journal of psoriasis and psoriatic arthritis, 6(1): 45-51.

32- Gopal, M. G.; Talwar, A.; BC, S. K., Ramesh, M.; Nandini, A. S &Meena, H. B. (2013). A clinical and epidemiological study of psoriasis and its association with various biochemical parameters in newly diagnosed cases. Journal of clinical and diagnostic research: JCDR, 7(12): 2901.

33- Alzeer, F.; AlOtair, H &Aleisa, A. (2022). Epidemiology and cutaneous manifestations of psoriasis in Saudi Arabia: a narrative review. Clinical, Cosmetic and Investigational Dermatology, 347-355.

34- Dogan, S.; Mentesoglu, D.; Atakan, N &Simsek, H. (2019). A cross-sectional study investigating association of liver diseases in moderate to severe psoriasis patients, 14(1), 1-11.

35- Tang, X., & Chen, L. (2022). The risk of organ-based comorbidities in psoriasis: a systematic review and meta-analysis. AnaisBrasileiros de Dermatologia, 97, 612-623.

36- Badaoui, A.; Tounian, P &Mahe, E. (2019). Psoriasis and metabolic and cardiovascular comorbidities in children: A systematic review. Archives de Pediatrie, 26(2): 86-94.

37- Xu, L., Pan, Y., Tang, S., Bai, J., Wu, Y., Qiao, J., & Fang, H. (2022). Evaluation of Serum Proinflammatory Cytokine IL-17A and Tight Junction Protein Claudin-1 in Psoriasis. Contrast Media & Molecular Imaging, 5(9), 699-711.

38- Mousa, H. M., & Hassan, A. G. (2020). Interleukin-17 serum levels as a vital indicator of psoriatic Iraqi patients in Thi-Qar Province. EurAsian Journal of BioSciences, 14, 1101-1104

39- Michalak-Stoma, A.; Bartosińska, J.; Kowal, M.; Raczkiewicz, D.; Krasowska, D &Chodorowska, G. (2020). IL-17A in the psoriatic patients' serum and plaque scales as potential marker of the diseases severity and obesity. Mediators of inflammation, 55(3), 379-390.

40- Kyriakou, A.; Patsatsi, A.; Vyzantiadis, T. A &Sotiriadis, D. (2014). Serum levels of TNF-α, IL-12/23p40, and IL-17 in plaque psoriasis and their correlation with disease severity. Journal of immunology research,.23(6), 43-93.

41- Yilmaz, S. B.; Cicek, N.; Coskun, M.; Yegin, O &Alpsoy, E. (2012). Serum and tissue levels of IL-17 in different clinical subtypes of psoriasis. Archives of Dermatological Research, 304: 465-469.

42- Yousry, M.; Ibrahim, A. A.; Mohamed, E.; Azza, A. B &Sahar, T. (2009). Assessment of serum interferon gamma and interleukin-4 in psoriasis vulgaris.Dermatology and Allergology/PostępyDermatologii i Alergologii, 38(5): 858-863.

43- Ruterbusch, M.; Pruner, K. B.; Shehata, L & Pepper, M. (2020). In vivo CD4+ T cell differentiation and function: revisiting the Th1/Th2 paradigm. Annual review of immunology, 38: 705-725.

44- Walker, J. A & McKenzie, A. N. (2018). TH2 cell development and function. Nature Reviews Immunology, 18(2): 121-133.

45- Guenova, E.; Skabytska, Y.; Hoetzenecker, W.; Weindl, G.; Sauer, K.; Tham, M., ... &Biedermann, T. (2015). IL-4 abrogates TH17 cell-mediated inflammation by selective silencing of IL-23 in antigen-presenting cells. Proceedings of the National Academy of Sciences, 112(7); 2163-2168.

46- Onderdijk, A. J., Baerveldt, E. M., Kurek, D., Kant, M., Florencia, E. F., Debets, R., &Prens, E. P. (2015). IL-4 downregulates IL-1β and IL-6 and induces GATA3 in psoriatic epidermal cells: route of action of a Th2 cytokine. The Journal of Immunology, 195(4), 1744-1752.

47- Verghese, B.; Bhatnagar, S.; Tanwar, R &Bhattacharjee, J. (2011). Serum cytokine profile in psoriasis-a case–control study in a tertiary care hospital from northern india. Indian Journal of Clinical Biochemistry, 26: 373-377.

48- Bai, F.; Zheng, W.; Dong, Y.; Wang, J.; Garstka, M. A.; Li, R., ... & Ma, H. (2018). Serum levels of adipokines and cytokines in psoriasis patients: a systematic review and meta-analysis. Oncotarget, 9(1): 1266.

49- Zalewska, A.; Wyczołkowska, J.; Dziankowska-Bartkowiak, B &Sysa-Jedrzejowska, A. (2004). Interleukin 4 plasma levels in psoriasis vulgaris patients. Medical Science Monitor: International Medical Journal of Experimental and Clinical Research, 10(4), 156-62.

50- Erdal, B.; Albayrak, H.; AydınKurç, M.; Varol, G.; Yanık, M. E.; Erfan, G &Gulen, D. (2020). The role of serum Pro-and Anti-inflammatory cytokines as potential diagnostic markers for psoriasis.