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Serum soluble endoglin, IL-13, and IL-23 in psoriatic patients in Basra, Iraq

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Psoriasis (PsO) is a persistent inflammatory skin condition. PsO exhibits similar immunologic and genetic characteristics to other autoimmune inflammatory disorders, including rheumatoid arthritis and multiple sclerosis. Endoglin (ENG), a 180 kDa protein is located on the cells' surface and acts as a co-receptor for the Transforming Growth Factor (TGF)-β superfamily. Interleukin-13 (IL-13)is known for its importance as a modulator of Th2 immune responses. It was discovered that Th17 cells express the IL-13 receptor, and it has been observed that IL-13 inhibits the production of IL-17 in these cells. IL-23 promotes survival and proliferation of Th17 cells, and thus serves as a key master cytokine regulator for these diseases. The aim of the study was to evaluate serum level of ENG, IL-13, and IL-23 in PsO patients compared to the control group. We conducted a case control study in which 80 patients with PsO and 80 age and sex-matched apparently healthy controls were recruited. The serum level of the aforementioned markers was measured by ELISA. All the measured markers showed significant difference in patients with PsO when compared to control group. A positive significant correlation was observed between IL-13 and IL-23. sENG showed significant difference with treatment type, IL-13 and IL-23 showed significant difference with PASI score and treatment type. IL-23 also showed significant difference with PsO duration. The study suggested that ENG may have a potential role in the pathophysiology of PsO. IL-13 and IL-23 have significant relation with PsO; however, they did not have a correlation with ENG.

Keywords: serum soluble endoglin; interleukin-13; interleukin-23; inflammatory biomarkers.

Introduction

Psoriasis is a persistent inflammatory skin condition characterized by clearly defined red bumps or patches covered with white scales (Wu et al., 2023). The incidence of PsO varies considerably across different countries, with rates ranging from 0.24% in Taiwan and China, and to 8.5% in Norway. This condition affects around 60 million individuals, including both children and adults, globally (Michalek et al., 2017). In this dermatological condition, the outermost layer of skin, known as the epidermis, migrates towards the surface and then undergoes continuous shedding from the skin. The existing prevalence data is derived from a limited sample of only 20 nations, resulting in significant gaps in geographic coverage, particularly in low- and middle-income regions. The worldwide prevalence of PsO in adults varied from 0.51% to 11.43%, whereas in children it ranged from 0% to 1.37% (Michalek et al., 2017). A community-based study was conducted in Iraq, specifically in the governorates of Tikrit and Kirkuk. The study included 1545 people who were randomly selected. The results showed that the prevalence of Ps was 2.3% (Al Samarai, 2009). Novel CD4-positive T-helper (Th) cells, namely T-helper 17 (Th17) cells, play a significant role in the development of several disorders, including PsO (Blauvelt, 2007).

Naive T cells undergo differentiation into Th1, Th2, Th17, or T-regulatory cells in response to T-cell receptor activation and co-stimulation, as well as the production of particular cytokines by antigen-presenting cells (Stockinger & Veldhoen, 2007). Th17 cells are formed in peripheral tissue when exposed to external transforming growth factor (TGF)-β_1 and interleukin (IL)-6 in an inflammatory environment (Bettelli et al., 2006; Mangan et al., 2006). The intracellular transcription factors RORγt and Stat3 play a crucial role in the differentiation of Th17 cells from naïve T-cell progenitors (Ferber et al., 1996; Vermeire et al., 1997). TGF-β1 levels are increased in both the plasma and scales of PsO lesions. Additionally, keratinocytes secrete TGF-β_1 in response to injury or infection (Nickoloff & Naidu, 1994; Flisiak et al., 2002). The activation of dendritic cells, in conjunction with this release, is likely to be enough to produce Th17 cells that can cause inflammation in the skin (Li et al., 2004). Despite the presence of several distinctive and highly indicative signs, there are currently no recognized diagnostic criteria or standardized classification for the clinical range of cutaneous PsO. Contrary to other autoimmune disorders, histopathological examination and blood testing are typically not useful in diagnosing PsO. Occasionally, dermatopathological investigation can be useful in verifying the diagnosis of PsO. Therefore, in the majority of instances, the diagnosis of PsO relies mostly on recognizing patterns, which involves the morphological assessment of skin lesions and joints (Raychaudhuri et al., 2014).

Endoglin, often referred to as CD105, is a 180 kDa protein that is located on the surface of cells and acts as a coreceptor for ligands of the Transforming Growth Factor (TGF)-β superfamily. Endoglin is primarily expressed by activated endothelial cells and has a critical function in the process of (developmental) angiogenesis (Schoonderwoerd et al., 2020; Lateef et al., 2024). An extensive examination of CD105 distribution on melanocytic cells demonstrated a fluctuating expression of the protein in both benign and malignant lesions. Immunohistochemical (IHC) tests revealed that 50% of intradermal naevi, 25% of initial melanomas, and 34% of metastatic melanomas were stained by the anti-CD105 mAb MAEND3 (Altomonte et al., 1996). In addition, flow cytometric investigations have verified a low and varied expression of CD105 among a wide range of cultivated metastatic melanoma cells (Altomonte et al., 1996).

Membrane-bound endoglin expression by several cell types within the tumor microenvironment (e.g., CAFs, macrophages, immune, and endothelial cells) and how its secretion (either soluble and/or in EVs) contributes to tumor progression and metastasis in different cancer models make it a promising target for therapeutic strategies (González Muñoz et al., 2021).

Materials and methods

The study was approved by the Human Ethics Committee of Department of Biochemistry, College of Medicine, University of Basrah, Basrah, Iraq , Everyone who took part in the study was told about it and asked to sign a consent form. The patients were also guaranteed that their information would be kept private.

A total of 160 subjects were included in this questionnaire-based retrospective study, conducted from January 2024 to March 2024 at Al-Basrah Teaching Hospital, after approval of the study protocol by the local Institutional Review Board. The study divided participants

into two main groups: 80 patients with PsO as cases and 80 healthy individuals matched for both age and sex with cases. PsO patients attended the dermatology clinic in Al-Basrah Teaching Hospital for medical consultation or routine check-ups. Exclusion criteria comprised diabetic mellitus, liver diseases, renal diseases, tumors and congestive heart failure. Each participant completed a thorough questionnaire comprising demographic data (age, gender, type of treatment, whether topical, systemic [methotrexate / biologic], or phototherapy, and duration of PsO). Four ml of venous blood were collected from each individual and placed in a gel tube free of anticoagulant with clot stimulator. The samples were centrifuged at 4000 rpm for 10 minutes and the serum were transferred into two separate 1.5 mL tubes and stored in a deep freeze for later assessment of the biochemical markers.To estimate the serum level of sENG, IL-13, and IL-23, a sandwich-ELISA technology was used. The level was determined based on the instruction of the manufacturer for sENG (Sunlong, China, REF SL2592Hu), IL-13 (Sunlong, China, REF SL0974Hu), and IL-23 (Sunlong, China, REF SL0989Hu).

In this study, the program SPSS Statistics version 23 was employed for data analysis. The data were presented using mean ± standard deviation and percentages. To compare continuous data between two groups we utilized the independent Student t-test, while to analyze categorical data we utilized the χ^2 test. Pearson correlation was used to assess the correlation coefficient (r). A P-value of less than 0.05 was considered to indicate statistical significance.

Results

Table 1 shows the demographic, clinical and biochemical data of the participants. There was no significant difference between cases and controls in age and gender ($P > 0.05$). Males contribute more than half of the participants (61.3% and 58.8% for controls and cases, respectively). A highly significant difference between controls and psoriatic patients in the levels of sENG (1086.87 ± 201.14 pg/mL for controls and 1346.1 ± 493.44 pg/mL for cases), IL-13 (32.80 ± 17.66 pg/mL for controls and 58.77 ± 25.25 pg/mL for cases), and IL-23 (44.96 ± 8.07 pg/mL for controls and 49.81 ± 10.59 pg/mL for cases) ($P < 0.01$) was observed.

Table 1
Demographic, clinical, and biochemical data of the participants

Parameters	Controls, n = 80	Cases, n = 80	P-value
Age, years	31.8 ± 12.5	31.2 ± 11.5	NS
Gender, n (%)			
Male	49 (61.3%)	47 (58.8%)	NS
Female	31 (38.8%)	33 (41.3%)	
sENG, pg/mL	1087 ± 201	1346 ± 493	<0.01
IL-13, pg/mL	32.8 ± 17.7	58.8 ± 25.3	<0.01
IL-23, pg/mL	45.0 ± 8.1	49.8 ± 10.6	<0.01

Note: IL-13 – interleukin-13, IL-23 – interleukin 23, sENG – soluble endoglin.

Table 2 demonstrates the distribution of the biochemical parameters in accordance with the duration of disease, PASI score, and type of treatment. There were no significant differences ($P < 0.05$) in the mean level of sENG in cases in respect to the disease duration. However, there was a significant difference in the mean of sENG levels with respect to type of treatment ($P < 0.05$). Additionally, the study showed that there was no significant difference ($P > 0.05$) between the means of sENG level across the PASI score categories (<5, 5–10, and >10). According to the distribution of serum IL-13, the mean of IL-13 levels was significantly higher ($P < 0.05$) in psoriatic patients with a duration of disease of more than 5 years than in those with a duration of less than 5 years. In addition to that, the present study showed high significant difference in the mean of IL-13 levels with respect to type of treatment ($P < 0.01$). Furthermore, the mean levels of IL-13 have a highly significant increase according to the patient's PASI score ($P < 0.01$). Patients with a PASI score >10 have the highest mean value of IL-13 while the lowest value is for patients with a PASI score <5. Looking at the distribution of serum IL-23, the mean of IL-23 levels has no significance ($P > 0.05$) in psoriatic patients with a duration of disease of less than and more than 5 years. However, the study showed high significant difference in the mean of IL-23 levels with respect to type of treatment ($P < 0.01$). Furthermore, the mean levels of IL-23 showed a highly significant increase according to patient's PASI score ($P < 0.01$). Patients with a PASI score >10 had the highest mean value of IL-23 (53.29 ± 11.89 pg/mL) while the lowest value was for patients with a PASI score ranged from 5–10 (44.4 ± 5.0 pg/mL).

Table 2
Distribution of sENG, IL-13, and IL-23 based on disease duration, PASI score, and type of treatment of PsO

Parameter		sENG (mean ± SD), pg/mL	P-value
Duration of disease	≤5 years	1436 ± 456	NS
	>5 years	1303 ± 509	
Type of treatment	topical	1593 ± 540	<0.05
	systemic	1310 ± 500	
	topical and systemic	1243 ± 430	
PASI score	< 5	837	NS
	5–10	1451 ± 433	
	>10	1289 ± 523	
Duration of disease	≤ 5 years	50 ± 26	<0.05
	> 5 years	63 ± 24	
Type of treatment	topical	40 ± 19	<0.01
	systemic	67 ± 22	
	topical and systemic	63 ± 26	
PASI score	< 5	26.0	<0.01
	5–10	48 ± 23	
	>10	66 ± 24	
Duration of disease	≤ 5 years	49.2 ± 13.1	NS
	> 5 years	50.1 ± 9.3	
Type of treatment	topical	43.4 ± 5.2	<0.01
	systemic	51.3 ± 12.4	
	topical and systemic	52.1 ± 10.3	
PASI score	< 5	48.8	<0.01
	5-10	44.4 ± 5.0	
	>10	53.3 ± 11.9	

Table 3 illustrates a Pearson correlation of the study variables. There is a significant positive correlation of IL-23 with IL-13. Serum sENG correlates negatively and significantly with duration of PSO. The study also showed a positive and significant correlation between PASI score with IL-13 and IL-23 as shown in Figure 1 and 2.

Table 3
Pearson correlation of ENG, IL-13, and IL-23 levels with the variables of the study

Variables		sENG, ng/mL	IL-13, ng/mL	IL-23, ng/mL
Age	correlation coefficient	–0.090	0.041	0.069
	P	NS	NS	NS
Gender	correlation coefficient	0.017	0.039	0.137
	P	NS	NS	NS
Duration of PsO	correlation coefficient	–0.223	0.178	0.044
	P	<0.05*	NS	NS
PASI score	correlation coefficient	–0.049	0.373	0.411
	P	NS	<0.01**	<0.01**
sENG, ng/mL	correlation coefficient	1	0.093	0.084
	P	–	NS	NS
IL-13, ng/mL	correlation coefficient	0.093	1	0.371
	P	NS	–	<0.01**
IL-23, ng/mL	correlation coefficient	0.084	0.371	1
	P	NS	<0.01**	–

Discussion

Psoriasis is a skin disease that is caused by immune system dysfunction, and it is associated with various other diseases such as cardio-metabolic diseases, psoriatic arthritis, and mental health issues. This makes it a significant financial burden and a global health risk (Armstrong et al., 2021).

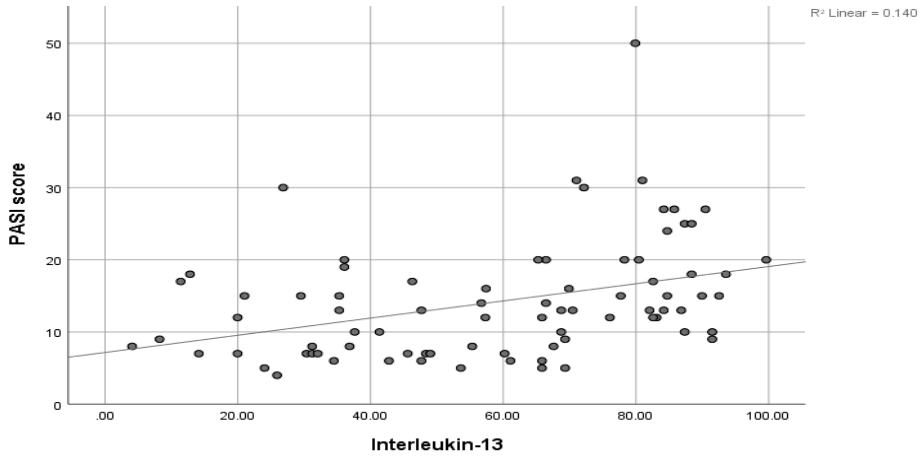

Fig. 1. Pearson correlation of IL-13 with PASI score

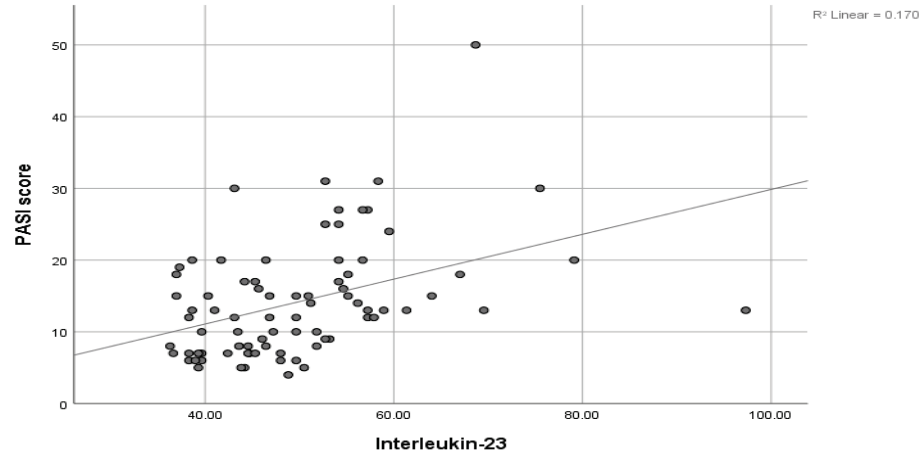

Fig. 2. Pearson correlation of IL-23 with PASI score

According to the data in the current study, the mean age of patients with PsO was found to be 31.2 ± 11.5 years, which is similar to the result obtained by Abdulridha et al. (2020) reported (35.1 ± 10.5 years) but it is contradictory to the findings of Maul et al. (2019) and Wilson et al. (2009). These differences can be explained by the variation of sample size and selection of participants. The current study revealed that the level of ENG rose significantly in patients with PsO when compared to healthy controls ($P < 0.01$). These findings were in accordance with the findings of Ibrahim et al. (2020), who stated that there was a significantly higher level of serum ENG in psoriatic patients.

Increased expression of ENG in psoriatic plaques has been described by Rulo et al. (1995) by the immune-histochemical method ,which found an increased expression in skin involved psoriatic plaques. ENG is mainly expressed on the endothelial cell's luminal membrane, activated monocytes and macrophages and syncitiothrophoblasts. It has been shown that ENG is considerably upregulated under inflammatory conditions such as PsO and in conditions with endothelial cell proliferation such as granulation tissue and cutaneous melanoma (Rulo et al., 1995; Hamad et al., 2024). However, further studies on serum soluble ENG level are recommended to evaluate its role as a diagnostic or prognostic tool for psoriatic patients. The result of this study revealed that there was no statistical difference in the mean value of sENG with respect to the duration of PsO. However, a statistically significant difference was obtained with respect to the type of treatment and serum level of ENG. This study found that the mean level of serum ENG differs significantly with type of treatment; patients on topical treatment had the highest values of serum ENG, while patients on topical and systemic treatment had the lowest values. As for IL-13, the current study found that the mean level of IL-13 in patients' serum was significantly higher than the controls' serum ($P < 0.01$), in contrast to the findings of Hijnen et al. (2013) , who found a decreased expression of IL-13 in psoriatic patients when compared to Atopic dermatitis patients. However, Hijnen, DirkJan did not compare their findings with a healthy population, which may be the cause of this difference. Furthermore, IL-13 has significantly increased with duration of disease and PASI score and differ with type of treatment. A study by Hsieh et al. (2024) found that the decrease in PASI score is strongly correlated with IL-13 decrease, and suggests that IL-13 levels could represent the effectiveness of biological treatment on psoriatic patients. Further study of IL-13 pathways during these stages is recommended. In respect to IL-23, our study showed that IL-23 levels in patients with PsO were significantly higher than controls. Similar findings were noted by Coimbra et al. (2010). Another study by Fotiadou et al. (2015) showed similar results compared to control and noted a significant increase in IL-23 level in patients with active disease compared to patients with stable PsO suggesting a possible role of IL-23 in the activity of PsO. Additionally, IL-23 showed a significant increase with increased PASI score and with different treatment types.

Conclusion

The main finding of our study was that serum level of sENG, IL-13, and IL-23 were significantly higher in PsO patients than healthy controls. The study found that ENG level was significantly higher in PsO patients suggesting a significant role in the development of PsO. The study also showed that ENG level significantly varied with different treatment type. IL-13 and 23 were significantly higher in PsO patients, and their levels were significantly affected by disease duration, PASI score, and type of treatment.

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