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Association Between Interleukin 27 and Different Types of Autoimmune and Dermatological Conditions A Systematic Review

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Abstract:

Numerous Th1/Th17-mediated inflammatory disorders have been linked to the immunological importance of interleukin 27. Numerous autoimmune and dermatological disorders have been associated with variations in interleukin 27 concentrations. The current study aimed to assess the relationship between serum levels of interleukin 27 and different types of skin diseases. For relevant articles, we searched Cochrane, Web of Science, PubMed, and SCOPUS. We utilized a strategy for our search by combining these keywords: (" interleukin 27 " OR " IL-27 " OR "cytokine") AND (" psoriasis " OR " vitiligo " OR " multiple sclerosis " OR " keratoacanthoma " OR " squamous cell carcinoma "). Quality assessment of the included studies was evaluated according to Cochrane's risk of bias tool. We found that the levels of serum interleukin 27 affected by different skin diseases as individuals suffering from squamous cell carcinoma, keratoacanthoma, systemic sclerosis, basal cell carcinoma, and psoriasis showed substantially higher levels of serum interleukin 27 than healthy participants. However, vitiligo patients showed a significant reduction in levels of serum interleukin 27 than the control cohort. In conclusion, there is an association between the serum levels of interleukin 27 and several skin diseases such as vitiligo, squamous cell carcinoma, keratoacanthoma, systemic sclerosis, basal cell carcinoma, and psoriasis. Squamous cell carcinoma, keratoacanthoma, systemic sclerosis, basal cell carcinoma, and psoriasis were associated with high levels of serum interleukin 27.

Keywords: Interleukin 27; psoriasis; vitiligo; multiple sclerosis; keratoacanthoma; squamous cell carcinoma.

1. Introduction

Interleukin 27 is a kind of the cytokine superfamily interleukin 12/ interleukin 6, which shares receptors and performs related inflammatory actions [1]. Secreted interleukin 27 attaches to a heterodimeric receptor complex formed up

of interleukin-27 receptor alpha (also known as TCCR or WSX-1) and gp130 [2]. Specific to interleukin 27, interleukin 27Rα appears mainly on the surface of inflammatory cells such as B cells, macrophages, dendritic cells, microglia, natural killer cells, mast cells, neurons, naive CD8+ and CD4+ T cells, and radial glia [3].

Interleukin-27 is a heterodimeric cytokine made up of the 24 kDa Epstein Barr Virus-induced gene 3 (EBI3) protein and the 28 kDa interleukin 27p28 subunit. Interleukin 27 subunits are largely generated in antigen-presenting cells following the activation of CD40, complement, interferon (IFN) receptors, and Toll-like receptors, proving that interleukin 27 is an important response to a range of inflammatory signals [4].

Antigen-presenting cells and epidermal keratinocytes, including dendritic and macrophage cells, release interleukin 27 into the skin [5]. Cutaneous interleukin 27 controls Th1-mediated inflammation, suppresses interleukin 17 cell formation, modifies Th2 development and cytokine production, and inhibits Th1-mediated inflammation. As a result, interleukin 27 has been proposed as a possible therapeutic molecule for the management of allergy diseases caused by Th2 cells. However, interleukin 27's therapeutic potential as a T-cell modulator is limited since it also stimulates keratinocyte activation and keratinocyte-derived inflammation [6]. Specifically, interleukin 27 increases the synthesis of CXCL10, increases MHC class I expression, sensitizes TNF-α signaling, and stimulates the activator of transcription-3 and -1 (STAT3 and STAT1) pathways and the signal transducer in keratinocytes [7].

Among the cytokines under investigation for potential therapeutic uses, interleukin 27 has been demonstrated to have dual effects on tumor growth and suppression, based on the features of the targeted neoplasm [8]. Numerous studies have shown that interleukin 27 inhibits cancerous cells both directly and indirectly [9]. Research on pediatric leukemias, multiple myeloma (MM), lymphomas, prostate cancer, neuroblastoma, melanoma, ovarian cancer (SKOV3 cell line), non-small-cell lung cancer (NSCLC), colon cancer, squamous cell carcinoma (SCC), and esophageal cancer has demonstrated the ability of this cytokine in tumor restriction [10].

TNF-, interleukin 6, and IL-1 are examples of cytokines that play important roles in the pathophysiology of vitiligo. It has been proposed that interleukin 27 is a cytokine that both inhibits and promotes inflammation. Changes in interleukin 27 concentrations have been linked to several auto-immune conditions, including psoriasis, rheumatoid arthritis, vitiligo, and multiple sclerosis [11].

The current systematic review aims to assess the relationship between serum levels of interleukin 27 and different types of skin diseases.

2. Methods

We performed this study based on the PRISMA guidelines and recommendations [12].

2.1.Information Sources and Search Strategy

We utilized a strategy for our search by combining these keywords: (" interleukin 27 " OR " IL-27 " OR "cytokine") AND (" psoriasis " OR " vitiligo " OR " multiple sclerosis " OR " keratoacanthoma " OR " squamous cell carcinoma "). Regarding the sources of data, we utilized Web of Science, PubMed, Cochrane Library, and SCOPUS databases in the search process. We searched these databases till February 2024.

2.2.Study selection

We started by screening the titles and abstracts. We then carried out a full-text screening. Finally, we choose the qualifying articles by the following eligibility requirements: Case cohort: Adult individuals suffering from skin diseases such as vitiligo, psoriasis, systemic sclerosis, basal cell carcinoma, keratoacanthoma, and squamous cell carcinoma, Control cohort: Healthy individuals without skin diseases, Intervention: Assessing the levels of serum interleukin 27, and Outcome: Serum levels of interleukin 27 in the patients and controls.

Inclusion criteria

We included papers that had our eligibility criteria which were recent studies above 2010, studies that included both males and females, studies that evaluate the levels of serum interleukin 27, double-arm studies that have case and control cohorts, and articles in English. We chose observational studies and blind or non-blind and non-randomized or randomized controlled clinical trials (RCTs)

Exclusion criteria

We excluded reviews, surveys, abstracts, and meta-analyses. Also, we excluded single-arm studies that assessed only one group and studies in languages other than English.

2.3.Quality assessment

Since we involved only observational studies, we used the Cochrane risk of bias (ROB) assessment, which evaluates 14 categories in each clinical study 13. Each study got a score from 1 to 14 and the overall average score will be calculated.

2.4.Data extraction

Two different categories of data were taken from the included papers. The first type includes the demographic information about the patients involved and the baseline data for our results. The second category was data of quality assessment. Microsoft Excel was used to carry out the data collection process [14].

3. Results

Our search results are demonstrated in the PRISMA flow chart (Figure 1). We involved five studies [2,5,7,8,11] that met the inclusion criteria of our systematic review. Our study involved 412 individuals divided into two cohorts; the case cohort which involved 243 patients and the control cohort which involved 169 healthy individuals. The case cohort included 177 females and 116 males while the control cohort included 79 females and 72 males. The mean age of the included participants in the keloid cohort was 40.6 years while that of the control cohort was 39.8 years. **Table 1** demonstrates the characteristics of the involved studies and patients**.**

Table 1: The characteristics of the involved studies and patients.

Study ID	**Country**	**Study design**	**Sample size**		**Age, years (mean, SD)**		**Male (N)**		**Female (N)**	
			Case	Control	Case	Control	Case	Control	Case	Control
Ghahartars 2018	Iran	Across-sectional analytical study	60	28	67.60±12.82	67.60±12.82	45	18	15	10
Hosseini 2020	Iran	Case-control	79	45	36.37 ± 14.7	35.06 ± 11.5	32	18	47	27

		study								
Kambayashi 2013	Japan	Case-control study	10	18	NR	NR	NR	NR	NR	NR
Shibata 2010	Japan	Case-control study	42	39	51.8±11.9	49.8±9.4	33	32	9	7
Yoshizaki 2011	Japan	Across-sectional analytical study	52	39	47±14	46±17	6	4	46	35

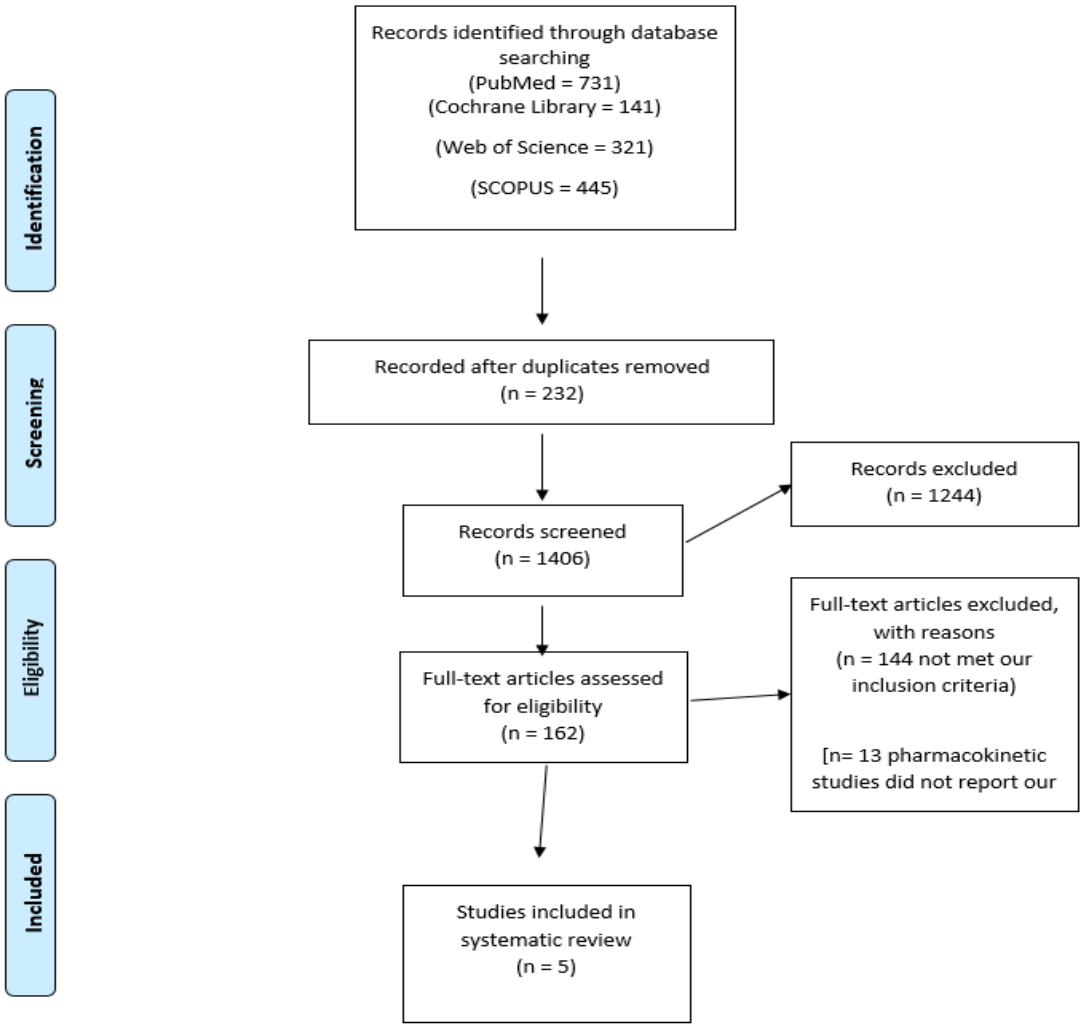

Figure 1: PRISMA flow diagram.

Since we included five observational studies [2,5,7,8,11], we assessed their quality using Cochrane's tool. Cochrane's tool indicated that the observational studies' mean score was 10.6 out of 14. The quality evaluation of the observational studies is shown in detail in **Table 2.**

Table 2: The quality assessment of the included studies.

	[8]	**[11]**	**[5]**	**[7]**	**[2]**
1. Was this paper's goal or research question made clear??	1	1	1	1	1
2. Was the target population for the study well-defined and specified?	1	1	1	1	1
3. Was at least 50% of eligible individuals participating?	1	1	1	1	0
4. Did all the participants come from the same or comparable populations, and did they all participate over the same period?	0	1	1	1	1
5. Was there a power description, an explanation for sample size, or estimates of effect and variance?	0	0	0	0	0
6. Were the exposure(s) wanted to be measured before the outcome(s) were determined for the analysis in this paper?	1	1	1	1	1
7. Was the duration such that, if a relationship between outcome and exposure existed, one could fairly anticipate seeing it?	1	1	1	1	1
8. Was the relationship between different exposure levels and outcomes for exposures that can change in quantity or degree (such as exposure categories or exposure measured as a continuous variable) examined in the study?	1	1	1	1	1
9. Were the exposure measures, or independent variables, well-defined, legitimate, dependable, and applied similarly to every study participant?	1	1	1	1	1
10. Was there a repeated evaluation of the exposure(s) throughout time?	0	0	1	0	0
11. Were the dependent variables, or outcome measurements, properly defined, dependable, valid, and applied similarly to every study participant?	1	1	1	1	1
12. Were the people evaluating the results blinded to the participants' exposure status?	*	*	*	*	*
13. Was the follow-up loss 20% or less of the baseline?	1	1	1	1	1
14. Has the impact of important potential confounding variables on the link between outcome(s) and exposure(s) been quantified and statistically adjusted?	1	0	1	1	1
Total score (out of 14)	10/14	10/14	12/14	11/14	10/14

Table 3: The changes of interleukin 27 levels in various skin diseases.

Author	Disease	Interleukin 27 levels
Hosseini et al. (2020) [11]	Vitiligo	The serum levels of interleukin 27 varied significantly between healthy volunteers (7097.7 ±1502 pg/mL) and patients with vitiligo (5267.8 ±399 pg/mL).
Ghahartars et al. (2018) [8].	Nonmelanoma skin cancer (NMSC)	The study included 28 healthy, age- and gender-matched controls and a total of 60 NMSC patients. The analysis revealed that interleukin 27 serum levels were considerably lower in controls compared to NMSC patients (0.0008 vs 0.0134 ng/ml; p <0.001). Patients with basal cell carcinoma and squamous cell carcinoma did not have different serum levels of interleukin 27 in the subgroup analysis based on pathologic diagnosis (P =1.000). On the other hand, they found that, compared to controls, squamous cell carcinoma cases had higher levels of serum interleukin 27 (0.01342 versus 0.00081 ng/ml; P =0.002). Comparing the interleukin 27 serum levels of controls and basal cell carcinoma cases showed similar results (0.0008 versus 0.0100 ng/ml; p =0.033).
Kambayashi et al. (2013) [5].	Squamous cell carcinoma and keratoacanthoma	Keratoacanthoma and squamous cell carcinoma both had higher levels of interferon (IFN)-y producing cells, only keratoacanthoma showed higher levels of interleukin 27-producing cells. Furthermore, only in keratoacanthoma was the expression of pSTATI on cancer cells found in conjunction with interleukin 27. keratoacanthoma had a considerably higher number of interleukin 27-producing cells than squamous cell carcinoma (keratoacanthoma vs. squamous cell carcinoma; 94.7± 16 vs. 10.7±3.8) (p <0.05).
Yoshizaki et al. (2011) [2].	Systemic sclerosis (SSc)	Patients with SSc had significantly higher serum interleukin 27 levels (range from 21.5 to 188.8 pg/ml; median 74.1 pg/ml) than the control cohort (range 28.7–63.6 pg/ml; 41.8 pg/ml); p <0.005). In terms of the subgroups of SSc, patients with diffuse cutaneous SSc (dSSc) (range 37.1–188.8 pg/ml; median 83.0 pg/ml) and limited cutaneous SSc (lSSc) (range 21.5–112.1 pg/ml; median 65.3 pg/ml) had higher interleukin 27 levels than the controls (p<0.001 and p<0.01, respectively). Additionally, compared to individuals with lSSc, serum levels of interleukin 27 were substantially higher in dSSc cases (p <0.05). Levels greater than 62.9 pg/ml which was mean +2SD of samples of control serum were discovered in (53/91) 58% of all cases with SSc, 46% (21/46) of cases with lSSc, and 71% (32/45) of cases with dSSc. On the other

	hand, only 5% (1/20) of the control participants exhibited increased interleukin 27 levels
Shibata et al. (2010) [7]. Psoriasis	Psoriatic patients had substantially greater serum interleukin 27 levels compared to healthy controls (452 ±254 vs 318 ±239 pg/mL, p =0.005). They calculated the association between psoriasis areas and serum interleukin 27 level and severity index (PASI) scores, which measure the severity of psoriasis. They demonstrate a substantial association (r¼0.629, P =0.005) among these parameters in psoriatic individuals.

4. Discussion

There have been suggestions that interleukin 27 has both pro- and anti-inflammatory properties. Changes in interleukin 27 concentrations have been linked to several autoimmune and dermatological conditions. Although interleukin 27 was found to have a pro-inflammatory role in early searches, more recent data indicates that it inhibits a variety of cytokine production and immune cell proliferation [15]. These applications of cytokines are associated with their pro- or anti-inflammatory properties. The several functions of interleukin 27 are associated with the various tissues that are affected, the underlying mechanism, or the stage and type of autoimmune disorders [15].

In our study, we found that the levels of serum interleukin 27 affected by different skin diseases as individuals suffering from squamous cell carcinoma, keratoacanthoma, systemic sclerosis, basal cell carcinoma, and psoriasis showed substantially higher levels of serum interleukin 27 than healthy participants. However, vitiligo patients showed a significant reduction in serum interleukin 27 levels than the control cohort.

Wang et al. (2012) reported that patients with Vogt-Koyanagi-Harada disease (VKH) and active Behcet disease had significantly lower serum concentrations of interleukin 27 in the sera and supernatants of cultured peripheral blood mononuclear cells (PBMCs), as well as PBMCs' expression of interleukin 27 p28 mRNA [16]. Furthermore, Gaber et al. (2014) revealed that interleukin 27 levels in systemic lupus erythematosus (SLE) patients are much lower than in healthy controls. It was suggested that the concentration of interleukin 27 in vitiligo cases might be different based on these claims and the

findings of other research regarding the changed expression of interleukin 27 in the skin and autoimmune diseases [17]. Our review showed that vitiligo patients had lower serum levels of interleukin 27, which is consistent with earlier research in SLE and Behcet patients. This finding can be explained by a few likely processes. Initially, interleukin 27 directly inhibits Th17 growth by influencing dendritic cells and encouraging naïve CD4+ T-cells to produce IL-10. Th17 plays a role in vitiligo etiology by the synthesis of interleukin [17]. Through the suppression of transforming growth factor- (TGF-) and interleukin 6, which is reliant on the intracellular signaling protein STAT1, interleukin 27 prevents the development and production of Th17 cells [18].

In oncology and immunology, interleukin 27 gained popularity as researchers looked at its functions in carcinogenesis, its potential utilization as a biomarker for cancer, and the development of new immunological treatments. However, according to the kind of tumor, its stage, and numerous other identified and unidentified factors the outcomes of the studies that were done were largely controversial. In a study looking into the role of interleukin 27 in skin cancer development, according to Dibra et al. (2016) elevated interleukin 27 levels promote the development of papilloma in the skin, aid in the growth of mutant stem cells, promote angiogenesis, maintain the premalignant niche, and increase vessel density, all of which raise the risk of carcinogenesis [3]. However, Matsui et al. (2009) in their research on potential functions of interleukin 27 in squamous cell carcinoma of the head and neck found that the cytokine effects on natural killer cells led to extended survival, enhanced cytotoxic activity, and likely antibody-dependent cell-mediated cytotoxicity (ADCC) of these cells, which in turn led to superior antitumor responses [19].

The cytokine interleukin 27 is quite complex; it suppresses the immune system and reduces inflammation in Th17 cells while promoting Th1 development and activation. Therefore, it is critical to look at the involvement of interleukin 27 in conditions including psoriasis, inflammatory bowel disease, multiple sclerosis, and rheumatoid arthritis. Conditions that were formerly classified as Th1 type but are currently more widely identified as Th17 type. T cells produce IFN-g in response to interleukin 27 generated from antigen-presenting cells, and antigen-presenting cells in turn produce more interleukin 27 when

exposed to IFN-g. This suggests that there may be a self-sustaining inflammatory loop of interleukin 27/IFN-g, as seen by the study's positive relation between serum interleukin 27 and IFN-g levels. Our findings are supported by reports of increased interleukin 27 expression and a relationship between it and the severity of several so-called Th1/Th17 inflammatory disorders [7].

According to a recent study, activated fibroblasts have also been found to exhibit elevated interleukin 27R expression. SSc fibroblasts had much higher interleukin 27 expression than did healthy fibroblasts. Several cytokines, particularly interleukin 27, stimulate fibroblast activation in individuals with SSc, which could account for the increased expression of interleukin 27 in SSc fibroblasts [20]. Furthermore, additional fibroblast activation will probably be facilitated by the ligation of interleukin 27 to fibroblasts produced interleukin 27. Indeed, interleukin 27 stimulation elevated interleukin 27 expression on SSc fibroblasts, which was further augmented by interleukin 27 stimulation. Furthermore, the expression of interleukin 27 was raised in the epidermis of individuals with SSc, and interleukin 27 significantly promoted collagen formation and SSc proliferation [21].

Our systematic review has several limitations such as the presence of heterogeneity between the included articles, the small number of the involved studies, and the inclusion of only observational studies as our study did not include any randomized clinical trial. In addition, our review discusses different kinds of skin diseases, not specific ones which may affect the power of our evidence.

5. Conclusion

In conclusion, there is an association between the levels of serum interleukin 27 and several skin diseases such as vitiligo, squamous cell carcinoma, keratoacanthoma, systemic sclerosis, basal cell carcinoma, and psoriasis. Squamous cell carcinoma, keratoacanthoma, systemic sclerosis, basal cell carcinoma, and psoriasis were associated with high levels of serum interleukin 27. Vitiligo was associated with a low level of serum interleukin 27. Further studies and trials are needed to assess the correlation between the levels of interleukin 27 and different kinds of skin diseases.

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Conflicts of Interest: All authors declare no conflict of interest.

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