Type of the Paper (Systematic Review)

Interleukin-36 Level in Patients with Vitiligo: A Systematic Review

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Abstract:

Introduction: Research on the role of interleukin-36 in vitiligo, a chronic autoimmune skin ailment characterized by skin depigmentation caused by melanocyte loss, is rather restricted when compared to other autoimmune skin conditions such as psoriasis.
Aim of the study: To evaluate the role of the interleukin-1 family, especially interleukin-36 in the pathogenesis of vitiligo.
Subjects and Methods: We searched the Cochrane Library, Web of Science, PubMed, and Scopus for relevant articles. We utilized a strategy for our search by combining these keywords: (" interleukin-1 " OR " interleukin-1 " OR " interleukin-36 " OR " interleukin-36 ") AND (" pigmentary skin disorder " OR " vitiligo " OR " autoimmune disorder " OR " depigmenting disorder "). The quality assessment of the involved studies was evaluated using Cochrane's risk of bias tool.

Results: we found that the levels of tissues and serum interleukin-36 are elevated significantly in lesional skin and non-lesional skin of patients suffering from vitiligo. Additionally, Family members of interleukin-1 such as interleukin-36, interleukin-33, interleukin-1α, and interleukin-18 have a substantial impact on the pathogenesis of vitiligo.

Conclusions: Family members of interleukin-1 such as interleukin-36, interleukin-33, interleukin-1α, and interleukin-18 have a substantial impact on the pathogenesis of vitiligo. Interleukin-36 has an important impact on the etiology of vitiligo due to its powerful pro-inflammatory effects. It is strongly connected with the severity of the disease and is more present in the tissue and serum of individuals suffering from vitiligo than in healthy people.

Keywords: Interleukin-1; Interleukin-36; vitiligo; autoimmune disorder; depigmenting disorder.

1. Introduction

An acquired depigmenting disorder called vitiligo is brought on by the selective apoptosis of melanocytes. It is distinguished by milky-white skin patches of varying sizes and shapes [1]. It is the most common depigmentary condition, affecting around 0.5-1% of people globally. Vitiligo can occur at any age, although half of all patients get it before the age of 20 [2]. Usually, vitiligo appears as perfectly formed, milk-white, amelanotic patches and macules encircled by healthy skin [3]. Lesions are usually symmetrical and can appear anywhere on the body. The face, axillae, nipples, hands' dorsal surfaces, the anogenital area, elbows, knees, shins, and feet' dorsal surfaces are among the common locations [4].

The specific cause of vitiligo is uncertain. It is frequently related to many autoimmune disorders. There are several views about its pathogenesis, and the cause is complicated [5]. It is distinguished by inadequate penetrance, genetic variability, and many susceptibility loci. Family and other twin investigations have revealed that inheritance is complex, involving both environmental and genetic influences [6]. Vitiligo is usually diagnosed based on clinical signs and symptoms; however, a light examination can sometimes assist in distinguishing vitiligo from other hypopigmented or depigmented illnesses [7]. A histological examination of the skin indicates a lack of melanocytes and total epidermal pigmentation loss [8].

Vitiligo is an autoimmune illness that causes depigmentation through T cells. Vitiligo has been linked to altered cytokine concentrations, including interleukin-2, IFN-γ, interleukin-10, interleukin-13, interleukin-17, and TGF-β, produced by helper and regulatory T cells [9]. Interleukin-17 interacts with keratinocytes, macrophages, and fibroblasts. It also increases the expression of interleukin-6 and interleukin-1. Interleukin-1 is a pro-inflammatory main cytokine [10]. It connects the innate and acquired immune systems, providing synergistic host defense activity in the skin [11]. There are two types of interleukin-1: interleukin-1α and interleukin-1β. The interleukin-1 family of cytokines consists of 11 members: 7 proinflammatory agonists (interleukin-1β, interleukin-1α, interleukin-36α, interleukin-18, interleukin-36β, interleukin-33, interleukin-36γ) and 4 known or putative antagonists (interleukin-

1R antagonist (interleukin-1Ra), interleukin-38, interleukin-37, and interleukin-36Ra) [12].

Keratinocytes produce interleukin-36α, interleukin-36Ra, interleukin-36γ, and interleukin-36β, which increase during inflammation [13]. Interleukin-36 promotes the synthesis of chemokines that attract T lymphocytes, neutrophils, and macrophages [14]. Interleukin-36 stimulates monocytes and myeloid dendritic cells, leading to the synthesis of interleukin-1β and interleukin-6. Interleukin-36 cytokines are increasingly linked to inflammatory disorders [15]. Associated diseases involve rheumatoid and psoriatic arthritis, inflammatory bowel disease (IBD), and numerous inflammatory and infectious skin conditions. Psoriasis is the most common skin condition related to interleukin-36. Interleukin-36γ has been established as a particular biomarker [16]. In our systematic review, we aim to evaluate the role of the interleukin-1 family, especially interleukin-36, in the pathogenesis of vitiligo.

2. Methods

We performed this study based on the PRISMA guidelines and recommendations [17].

2.1. Information Sources and Search Strategy

We utilized a strategy for our search by combining these keywords: (" interleukin-1 " OR " interleukin-1 " OR " interleukin-36 " OR " interleukin-36 ") AND (" pigmentary skin disorder " OR " vitiligo " OR " autoimmune disorder " OR " depigmenting disorder "). Regarding the sources of data, we utilized the Web of Science, PubMed, Cochrane Library, and SCOPUS databases in the search process. We searched these databases till May 2024.

2.2. Study selection

We started by screening the titles and abstracts. We then carried out a full-text screening. Finally, we chose the qualifying articles by the following eligibility requirements: Case cohort: Adult individuals suffering from vitiligo, Control cohort: Healthy individuals without skin diseases, Intervention: Assessing the levels of interleukin-1 family, especially interleukin-36, and Outcome: Levels of interleukin-1

family, especially interleukin-36, in the patients and controls.

Inclusion criteria

We included papers that met our eligibility criteria, which were recent studies above 2010, studies that involved both males and females, studies that evaluated the levels of serum interleukin-36, double-arm studies that had 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 [18]. 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 involved papers. The first type involves the demographic information about the patients involved and the baseline data for our results. The second category was data on quality assessment. Microsoft Excel was used to carry out the data collection process [19].

3. Results

3.1. Summary of the involved studies

Our search results are demonstrated in the PRISMA flow chart (**Figure 1**). We involved four studies [20–23] that met the inclusion criteria of our systematic review. Our study involved 224 individuals divided into two cohorts: the case cohort, which involved 151 patients and the control cohort, which involved 73 healthy individuals. The case cohort involved 96 females and 55 males, while the control cohort involved 38 females and 35 males. The mean age of the

involved participants in the vitiligo cohort was 36.6 years, while that of the control cohort was 37.5 years. **Table 1** demonstrates the characteristics of the involved studies and patients.

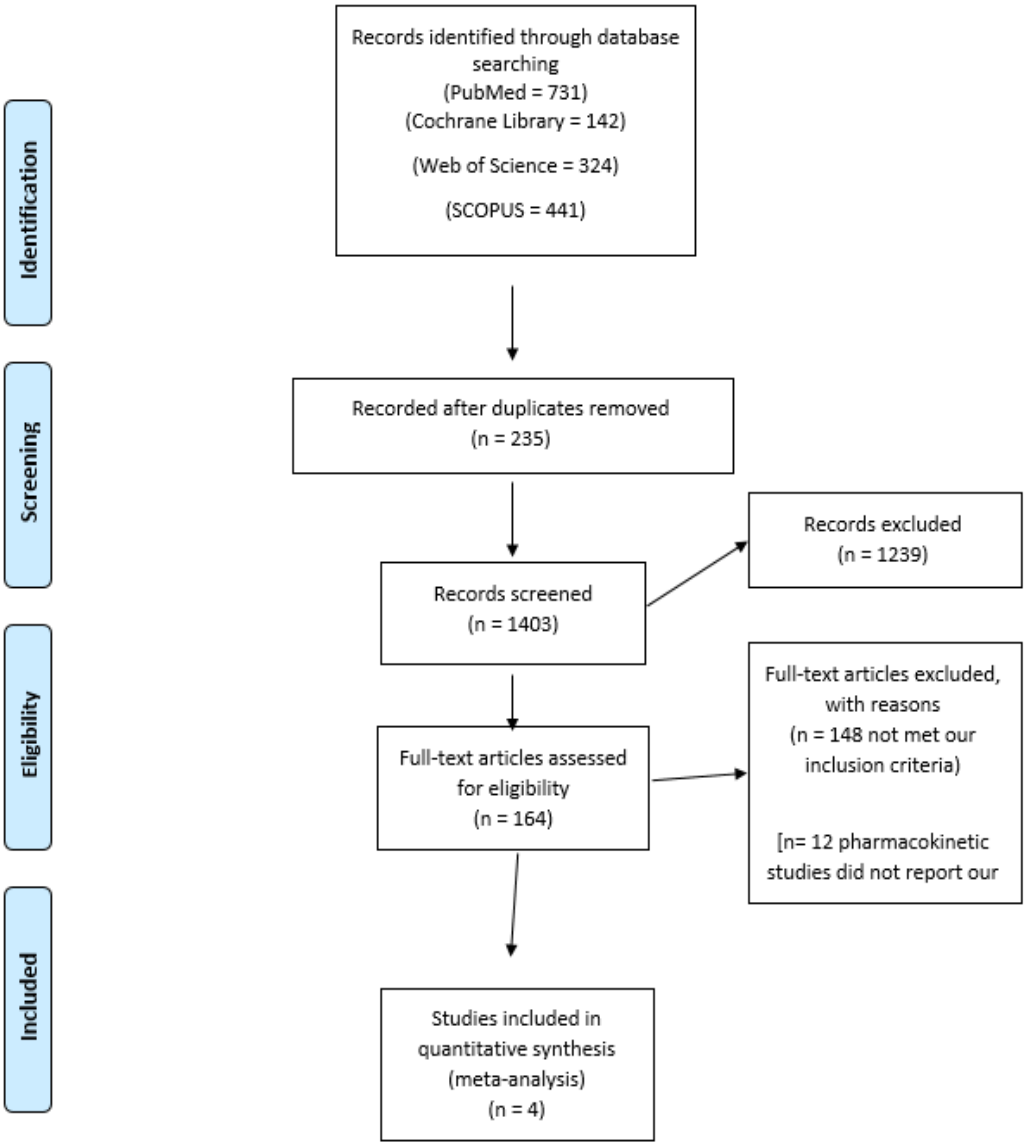

Figure 1: Literature search's PRISMA flow diagram.

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
Atef 2022	Egypt	Cross-sectional analytical	41	5	34.71±16.89	36.40±19.40	12	3	29	2
Nieradko-Iwanicka 2023	Poland	Case-control	50	38	43.1 ±16.2	45.31±15.81	15	16	35	22
Li 2014	China	Case-control	10	10	39.9 ±4.4	39.9 ± 4.4	5	5	5	5
Tu 2003	China	Case-control	50	20	29.22	29.25	23	11	27	9

3.2. Results of quality assessment

Since we involved four observational studies [20–23], we assessed their quality using Cochrane's tool. Cochrane's tool indicated that the observational studies' mean score was 10.57 out of 14. The quality evaluation of the observational studies is shown in detail in **Table 2.**

Table 1: The quality assessment of the involved studies.

	Atef 2022	**Nieradko-Iwanicka 2023**	**Li 2014**	**Tu 2003**
1. Was the paper's goal or research question made clear??	1	1	1	1
2. Was the target population for the study well-defined and specified?	1	1	1	1
3. Was at least 50% of the eligible individuals participating?	1	1	1	1
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
5. Was there a power description, an explanation for sample size, or estimates of effect and variance?	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
7. Was the duration such that, if a relationship between outcome and exposure existed, one could fairly anticipate seeing it?	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
9. Were the exposure measurements, or independent variables, appropriately defined, valid, trustworthy, and administered to each research subject identically?	1	1	1	1

10. Was there a repeated evaluation of the exposure(s) throughout time?	0	0	1	0
11. Were the dependent variables, or outcome measurements, properly defined, dependable, valid, and applied similarly to every study participant?	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
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
Total score (out of 14)	10/14	10/14	12/14	11/14

*Key: 0 = No, 1 = Yes, N/A = Not applicable, * = Not reported.*

3.3. Systematic review

Atef et al. conducted a cross-sectional study to assess the interleukin-36 expression by tissues in lesions of vitiligo and normal skin. They found that there was no substantial difference between the levels of interleukin-36 in the skin lesions and nonlesional skin of participants who suffered from vitiligo. Additionally, they prove that varied healthy controls showed no expression of interleukin-36 [20].

Nieradko-Iwanicka et al. tried to assess the serum levels of interleukin-1 and interleukin-18 in healthy volunteers and patients suffering from vitiligo. The study involved 38 healthy, age- and gender-matched controls and a total of 50 patients suffering from vitiligo. The analysis revealed that the mean concentration of interleukin-1α was 0.13 ±0.535 pg/mL in the vitiligo cohort and 0.51 ± 1.51 in the control cohort patients. Between those participating in the study cohort and the control cohort, there was no statistically substantial variation in concentrations of interleukin-1α ($p > 0.05$). The mean interleukin-18 concentration in the study cohort's patients was 141.05 ±136.33 pg/mL, whereas the control cohort's patients had a mean concentration of interleukin-18 of 137.33 ±105.83 pg/mL. Between those participating in the study cohort and the control cohort, there was no statistically substantial variation ($p > 0.05$) [21].

Li et al. conducted an article to determine the role of a family member of the interleukin-1, which is interleukin-33, in individuals suffering from vitiligo. They found that the interleukin-33 expression was considerably elevated in the skin lesions of the vitiligo cohort compared to the perilesional skin ($p < 0.01$, increased 1.9-fold) and healthy participants' cohort skin ($p < 0.01$, increased 4.7-fold) [22].

Tu et al. aimed to evaluate the potential roles of tumor necrosis factor-alpha (TNF-a), granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-1, interleukin-6, beta (interleukin-1 b), and interleukin-8 in the cause of vitiligo. The findings demonstrated that the patients with segmental vitiligo had levels of serum GM-CSF and interleukin-6 that were substantially higher than those of normal controls for both focal type and generalized type vitiligo, as well as interleukin-1 b from the generalized type [23].

4. Discussion

Vitiligo presents as well-circumscribed, depigmented macules and patches with convex borders, surrounded by normal skin, which is slowly progressive. Interleukin-36 is a group of cytokines that belong to the interleukin-1 family. This family of cytokines has a substantial effect on the regulation of immune responses and inflammation [24]. The interleukin-36 cytokines involve interleukin-36α, interleukin-36β, interleukin-36γ, and interleukin-36Ra. Research on interleukin-36 and its role in immune regulation and inflammation continues to evolve, with potential implications for the discovery of novel therapeutic approaches for inflammatory and autoimmune diseases [25]. Interleukin-36 cytokines have pro-inflammatory properties and can induce the synthesis of other pro-inflammatory chemokines and cytokines. They act on various immune cells, such as T cells, dendritic cells, and macrophages, to promote inflammation [26]. Interleukin-36 cytokines have been particularly implicated in skin inflammation and are associated with inflammatory skin conditions such as psoriasis. They promote keratinocyte proliferation and the production of pro-inflammatory cytokines in the skin, contributing to the development of psoriatic lesions [27].

Lesional skin from individuals with atopic dermatitis and inflamed skin from psoriasis patients both exhibit elevated expression levels of interleukin-36α and γ (28). Interleukin-36 stimulates T-cell proliferation and induces the release of interleukin-2. Additionally, interleukin-36 contributes to the pathophysiology of vitiligo by stimulating T cell proliferation and being essential in the Th0 cells'

conversion into Th1 cells, which generate interferon (IFN) production [28,29].

In our review, we found that the levels of tissues and serum interleukin-36 are elevated significantly in lesional skin and non-lesional skin of patients suffering from vitiligo. Additionally, family members of interleukin-1 such as interleukin-36, interleukin-33, interleukin-1α, and interleukin-18 have a substantial impact on the pathogenesis of vitiligo.

Regarding the role of the interleukin-1 family in vitiligo, Singh et al. observed that high levels of interleukin-1 have been linked to a number of autoimmune diseases, including vitiligo. Cytokines, such as interleukin-1, are generated by keratinocytes and lymphocytes and can cause melanocytes to undergo apoptosis. Additionally, they looked at the interleukin 1-α member's dose-dependent effect on melanocytes in vitro and discovered that interleukin 1-α is a strong inhibitor of melanocyte proliferation [30].

In healthy skin, interleukin-36 signaling contributes to immune surveillance and tissue repair processes. It regulates keratinocyte proliferation, differentiation, and barrier function, thereby maintaining skin homeostasis. However, dysregulated interleukin-36 signaling has been implicated in various inflammatory skin disorders, including psoriasis and atopic dermatitis. Certain studies have connected interleukin-36 to other inflammatory and autoimmune diseases, including psoriasis, generalized pustular psoriasis, Sjögren's syndrome, SLE, rheumatoid arthritis, allergic contact dermatitis, psoriatic arthritis, and osteoarthritis [31]. Blumberg et al. found a correlation between the expression of interleukin-36Ra and interleukin-36, which are expressed in psoriatic skin lesions, and the expression of other cytokines, including interleukin-17, TNF-, and IFN-. This suggests psoriasis might involve a positive gene expression loop [32].

Recent studies have suggested a potential link between interleukin-36 dysregulation and vitiligo pathogenesis. Elevated levels of interleukin-36 have been detected in the lesional skin of patients suffering from vitiligo, suggesting its involvement in disease progression. Mechanistically, interleukin-36 promotes the synthesis of pro-inflammatory chemokines and cytokines, causing the activation and recruitment of cytotoxic T cells. These activated T cells target melanocytes, resulting in their destruction and subsequent

depigmentation. Moreover, interleukin-36 may modulate the expression of melanocyte-specific antigens, further exacerbating immune-mediated damage. Additionally, interleukin-36-induced inflammation can disrupt melanocyte stem cell niche integrity, impairing melanocyte regeneration and contributing to depigmentation [20].

Matti et al. reported on the role of interleukin-36 in the cause of allergic contact dermatitis. Immunohistochemistry demonstrated that all three of the interleukin-36 agonists had increased levels in skin damaged by ACD and that these ligands were expressed in epidermal layers [33]. Derer et al. also supported a previous finding that interleukin 36R mRNA and interleukin-36 levels are elevated in arthritic joints. Previously, interleukin-36R and interleukin-36 were found in the synovial tissues of individuals suffering from osteoarthritis, psoriatic arthritis, and rheumatoid arthritis. RA and psoriatic arthritis had higher levels of interleukin-36 expression in their synovial tissues than osteoarthritis, and the main source of interleukin-36 was CD138+ plasma cells [34].

Ebrahim et al. examined the significantly higher levels of serum interleukin-33, another member of the IL1 family, in patients suffering from vitiligo when compared to controls. They concluded that interleukin-33 acts as an alarmin, causing melanocyte death in the skin of patients suffering from vitiligo [35]. Interleukin-33 was detected by immunofluorescence staining to be in the keratinocyte cytoplasm in the skin lesions of patients suffering from vitiligo but absent from the keratinocyte nucleus in normal skin. Interleukin-33 is moved from the nucleus of keratinocytes to the cytoplasm in vitiligo, according to Western blotting [22].

Our systematic review has several limitations, such as the presence of heterogeneity between the involved articles, the small number of involved studies, and the inclusion of only observational studies, as our study did not involve any randomized clinical trials. In addition, our review discusses different kinds of skin diseases and different family members of interleukin-1, not just interleukin-36, as research on the specific role of interleukin-36 in vitiligo is still emerging and not as extensive as in other skin conditions like psoriasis.

5. Conclusion

Family members of interleukin-1 such as interleukin-33, interleukin-36, interleukin-1α, and interleukin-18 have a substantial impact on the pathogenesis of vitiligo. Interleukin-36 has a substantial impact on the etiology of vitiligo due to its powerful pro-inflammatory effects. It is strongly connected with the severity of the disease and is more present in the tissue and serum of individuals suffering from vitiligo than in healthy people. Both lesional and nonlesional skin of patients suffering from vitiligo had greater expression of interleukin-36, suggesting a potential impact of interleukin-36 on the pathophysiology of vitiligo. Further studies and trials are needed to assess the relationship between the levels of interleukin-36 and vitiligo.

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