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Serum Level of Interleukin-38 in Vitiligo Patients and its Alterations After Narrowband Ultraviolet Light - B Phototherapy

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Abstract:
Background: Vitiligo is an autoimmune condition characterized by melanocyte loss and depigmented patches. Cytokines, especially those in the Th1 and Th17 pathways, play pivotal roles in its pathogenesis. Interleukin (IL)-38, a cytokine involved in immune regulation, may influence vitiligo progression and treatment outcomes, particularly in response to narrowband ultraviolet B (NB-UVB) therapy. **Aim:** This study aimed to assess serum IL-38 levels in vitiligo patients compared to healthy controls and evaluate correlations between IL-38 levels, disease severity indices, and treatment response to NB-UVB. Methods: A case-control study was conducted on 45 participants from the Dermatology Clinic at Benha University Hospitals. Group I included 15 patients with active vitiligo, Group II included 15 patients with stable vitiligo, and Group III included 15 healthy controls. Disease severity was assessed using Vitiligo Area Scoring Index (VASI) and Vitiligo Disease Activity (VIDA) scores, while quality of life was evaluated with the Dermatological Life Quality Index (DLQI). Serum IL-38 levels were measured pre- and post-NB-UVB therapy. **Results:** IL-38 levels were significantly elevated in vitiligo patients compared to controls ($P < 0.001$), with generalized vitiligo showing the highest levels. Post-treatment, IL-38 levels decreased significantly ($P = 0.003$), correlating with improvements in VASI scores ($P < 0.001$). IL-38 demonstrated strong sensitivity and specificity for predicting vitiligo (AUC = 0.891). **Conclusion:** Serum IL-38 is a potential biomarker for disease activity and treatment efficacy in vitiligo. Its role in modulating inflammation suggests therapeutic and diagnostic implications.

Key words : Vitiligo;Interleukin-38 (IL-38); Narrowband Ultraviolet B (NB-UVB) Phototherapy.

Introduction

A skin condition known as vitiligo causes depigmented patches and macules due to the selective loss of melanocytes. The autoimmune theory has gained the greatest traction among the several explanations put out for its origin. According to this view, the high concentration of CD8+ cytotoxic T cells (Tc) in vitiligo lesions is proof that these cells play a pivotal role in the death of melanocytes (1).

Research has shown that vitiligo patients had higher IL-17 levels and an increase in the number of T helper 17 (Th17) cells, suggesting that these cells have a role in the condition. Furthermore, vitiligo lesions are infiltrated by innate immune cells such as natural killer cells, macrophages, and inflammatory dendritic cells. This infiltration causes higher levels of cytokines linked to innate immunity, Th1 responses, and Th17 responses (2). Previous studies have shown that vitiligo patients have an imbalance of pro-inflammatory cytokines to anti-inflammatory cytokines (3).

B cells and keratinocytes are among the cell types that secrete interleukin (IL)-38, an innate immune cytokine that is related to the IL-1 family. IL-38 probably shares the antagonistic effects of IL-36Ra and IL-1Ra because of their structural similarity. Th1 and Th17 activation, as well as cytokine production (such as TNF-α, IL-1β, IL-6, and IL-17), may be suppressed when it binds to receptors on keratinocytes, macrophages, and T cells, inhibiting their agonistic ligands. There has not been nearly enough research on IL-38 levels in vitiligo patients compared to other autoimmune illnesses (4).

A crucial component of vitiligo treatment is phototherapy, namely narrowband ultraviolet B (NB-UVB). The efficiency and acceptable side effect profile of NB-UVB make it the ideal choice for widespread vitiligo. Repigmentation, decreased inflammatory cytokines, and increased T cell differentiation into regulatory cells are the mechanisms by which it exerts its effects. Doses of NB-UVB are usually adjusted according to the patient's reaction and given two or three times weekly (5).

Based on the Vitiligo Area Scoring Index (VASI) and Vitiligo condition Activity (VIDA) ratings both before and after NB-UVB treatment, the present research aimed to compare serum IL-38 levels in vitiligo patients with controls and to find a correlation between these levels and the severity of the condition.

Subjects and methods

From November 2022 to April 2023, researchers from Benha University Hospitals' Outpatient Clinic of Dermatology, Venereology, and Andrology performed this case-control

study. Fifteen patients with active vitiligo, fifteen with stable vitiligo, and fifteen healthy controls representative of both sexes and age were the 45 people that took part in the research. Patients of either sex who have non-segmental vitiligo were eligible to participate. People with systemic disorders, other skin issues, a history of recent treatments, and those who were pregnant or nursing were not allowed to participate. All subjects gave their informed permission after receiving ethical clearances.

In order to record the severity of vitiligo using the Vitiligo Area Scoring Index (VASI) and the Vitiligo Disease Activity (VIDA) scores, each participant completed a comprehensive clinical examination that included both local and global assessments (6). The Dermatological Life Quality Index (DLQI) (7) was used to assess quality of life, while photographs of lesions were documented. Minimal erythema dose (MED) testing informed the administration of narrowband UVB phototherapy, with dosage modifications made incrementally over a three-month period. We used an enzyme-linked immunosorbent assay (ELISA) kit for research purposes (Catalogue number: 201-12-7669, Baoshan District, Shanghai, China) to evaluate serum IL-38 levels. After three months of therapy, we repeated the tests to measure VASI score and IL-38 levels.

Statistical analysis

Statistical analysis was performed using SPSS version 28 (IBM, Armonk, NY, USA). Normality of quantitative data was assessed with the Shapiro-Wilk test and data visualization. Depending on normality, data were summarized as mean ± standard deviation or median and range, while categorical data were presented as frequencies and percentages. Group comparisons for quantitative data used the independent t-test or Mann-Whitney U test, and categorical data were analyzed using the Chi-square test. The Wilcoxon signed ranks test assessed pre- and post-treatment changes, while ROC analysis was conducted to evaluate IL-38's predictive value for vitiligo, with AUC values categorizing discrimination ability. Correlations were analyzed using Spearman's method, and IL-38 differences across parameters were assessed with the Mann-Whitney U test. Multivariate logistic regression predicted vitiligo with odds ratios and 95% confidence intervals, while multivariate linear regression examined predictors of VASI and DLQI. A p-value <0.05 was considered statistically significant.

Results

The studied groups were comparable regarding age (P = 0.233) and gender (P = 0.197). All patients presented with an acute onset of symptoms. Disease duration varied widely, with a median of 3.5 years. Most participants (80%) reported no family history of vitiligo. The median VASI and VIDA scores were 5 and 0.5, respectively, while the mean DLQI score was 15 ± 5. IL-38 levels were significantly elevated in patients compared to controls (P < 0.001) and decreased significantly after treatment (P = 0.003) (Table 1).

Table (1) Baseline IL-38 in the studied groups

IL-38		**Patients (n = 30)**	**Controls (n = 15)**	**P_1**
Before	Median (range)	30.27 (10.51 - 109.7)	15.14 (8.23 - 22.19)	**<0.001***
After	Median (range)	23.2 (10.03 – 42.99)	NA	**-**
P_2		0.003	-	

*Significant P-value; P1: Comparison of baseline IL-38 between groups; P2: Comparison of IL-38 before and after treatment; IL-38: Interleukin-38; P is significant if < 0.05; NA: Not applicable; Mann Whitney U test was used for between group comparison, while Wilcoxon signed ranks test was used for within group comparisons

VASI scores also showed significant improvement post-treatment (P < 0.001) (Table 2). ROC analysis for IL-38 yielded an excellent AUC of 0.891, with a cutoff of >22.19 yielding high sensitivity and specificity for predicting vitiligo. IL-38 levels correlated positively with disease duration, VASI, VIDA, and DLQI scores, but not with age. Patients with generalized vitiligo had significantly higher IL-38 levels than those with localized vitiligo (P < 0.001). Multivariate analysis indicated that each unit increase in IL-38 raised vitiligo risk by 24% (OR = 1.243, P = 0.002).

Table (2) VASI score before and after treatment in the patients' group

VASI	**Median (range)**	**P-value**
Before	5 (1.5 – 40.0)	**< 0.001***
After	2 (0.5 - 28)	

*Significant P-value; VASI: Vitiligo Area Scoring Index; P is significant if < 0.05; Wilcoxon signed ranks test was used

Discussion

The prevailing idea that explains why CD8+ T cells and Th17 cells destroy melanocytes in vitiligo, together with elevated levels of IL-17 in patients, is the autoimmune theory. Inflammation and cytokine abnormalities are also seen in vitiligo patients, which are innate immune cells such natural killer cells and macrophages (8).

Although its involvement in vitiligo is yet unknown, interleukin-38 is an anti-inflammatory cytokine that inhibits cytokine synthesis, therefore suppressing Th1 and Th17 responses (9). Treatment with phototherapy, particularly narrowband ultraviolet B (NB-UVB), is used for vitiligo because it helps with repigmentation by lowering inflammation and immunological activity, which is especially helpful for more widespread instances (10).

This case-control research set out to compare serum IL-38 levels in people with vitiligo to those in healthy controls, and to see if vitiligo severity and activity were correlated with IL-38 levels both before and after NB-UVB phototherapy. There were no statistically significant differences in the study groups with respect to gender or age.

The participants with vitiligo had an average age of 30 ± 14 years, and 66.7% of them were female. The results align with those of a research that found 63.3% of the participants to be female and an average age of 39.37 ± 13.13 years. The average age of the patients was 35.8 ± 10.8 years, and 66.7% of them were female, according to another research (12). Another research found that the average age was 33.3 years, and that 60% of the cases with vitiligo were in females (13). A newer research found that the average age of the patients was 36.00 ± 14.88 years, and that 62.3% of the patients were female (14). The bulk of the participants in the research were female (16 females and 5 males), and the average age was 28.24 ± 2.7 years (4). On the other hand, a different research indicated a patient mean age of 51.2 ± 12.5 years, with 51.4% of the participants being female (16), and another study indicated a higher mean age of 47.5 years (15).

This disparity arises because vitiligo does not discriminate based on gender or race and may manifest at any age (17). Also, there seems to be a bimodal distribution for the age of commencement; around one-third of cases begin at a young age (mean age 10.3 years), while the other two-thirds begin later in life (mean age 34.0 years), which might be due to environmental variables that delay the development of vitiligo (18).

It is possible that women are more likely to worry about the social implications of skin pigmentation changes, which may explain why this condition is more common in women (19).

A positive family history of vitiligo was reported by 20% of individuals in the present research. This is in line with previous research that found a comparable incidence of 11.31% and a positive family history in 11.6% of vitiligo patients, respectively (20). Nevertheless, a more substantial proportion of patients (36.7%) indicated a favorable family history in one research (22). The complicated and probably polygenic character of vitiligo inheritance may account for the diversity in these results (23).

The acrofacial and generalized regions were determined to be the most often impacted locations in the present investigation, with 36.7% of cases each. Thirteen percent of instances included the head and neck, ten percent involved the limbs, and ten percent involved the trunk. Consistent with other research, this study indicated that the face, acral regions, trunk, legs, neck, and arms were the most prevalent places (24,5,16).

Areas that are hyperpigmented under normal circumstances and those that are exposed to sunlight, such the face, dorsum manus, areola mammae, axilla, umbilicus, and genitalia, are the most prevalent sites where vitiligo develops. The Köebnerization reaction (2) often causes vitiligo on the extremities.

A significant improvement was seen when comparing VASI ratings before and after 36 phototherapy sessions in the present investigation. Previous studies have also shown a substantial decrease in the VASI score after 36 phototherapy sessions, which is in line with our current results (25, 26, 5).

While IL-38 levels in the control group were much lower following therapy, those with vitiligo had considerably greater levels to begin with. Consistent with earlier research, our study found that vitiligo patients had higher blood IL-38 levels than controls (4). The fact that vitiligo patients also had higher amounts of the anti-inflammatory cytokine IL-37 lends credence to the idea that IL-38 plays a role in the disease's pathophysiology, according to another research (27).

According to the latest research, vitiligo symptoms and indicators, such as Koebner's phenomenon, poorly defined boundaries, itching, and depigmented lesions that seem like confetti, are linked to elevated levels of IL-38 in the blood. Previous research has shown that vitiligo activity is connected to an increase in the infiltration of inflammatory cells and an upregulation of Th1 (TNF-α and interferon-γ) and Th17 (IL-17A) cytokines, and our results are in line with those findings. This provides further evidence that monocytes and keratinocytes may

be stimulated to express IL-38 in active vitiligo in response to the elevated pro-inflammatory cytokine environment, which aims to mitigate excessive inflammation.

The present research also found a positive correlation between IL-38 levels and illness duration, VASI, VIDA, and DLQI, which may indicate that higher IL-38 levels are linked to a more severe disease and its effect on quality of life. Furthermore, IL-38 proved to be an exceptionally dependable biomarker for vitiligo, because to its great specificity and positive predictive value. These results are in line with other studies that found elevated IL-38 levels in disease-active individuals, which were shown to be significantly correlated with the severity of the illness (4). It is possible that elevated IL-38 serum levels in vitiligo patients represent an immune system mechanism that tries to reduce the cytotoxic onslaught on melanocytes, particularly in active or severe instances, by limiting Th1 and Th17 activation.

Another research, however, indicated that IL-38 levels were much lower in vitiligo patients than in healthy controls, which is in contrast with the first findings (14). Differences in disease biology, sample sizes, and genetic predispositions might account for these inconsistencies.

In vitiligo patients, an enhanced blood level of IL-10, a Th2 cytokine that suppresses pro-inflammatory Th1 cytokines like TNF-α, was seen, which is comparable to a previous study's findings (3). Although this reaction seems inadequate to completely regulate disease activity, the researchers hypothesized that increased IL-10 levels may constitute an effort to combat Th1-driven inflammation.

Patients with RA also have higher levels of IL-38 and other anti-inflammatory IL-1 family members, including IL-1Ra, IL-37, and IL-36Ra, in their blood and synovial membranes (30). As shown in diseases such as ST-elevated myocardial infarction (STEMI), where IL-38 levels peak and correlate with the amount of inflammation (31)—IL-38 might either be a biomarker reflecting the severity of the illness or play a role in mitigating its effects.

Serum IL-38 levels are greater in pustular psoriasis patients compared to healthy controls in psoriasis, another inflammatory dermatosis mediated by the immune system (32). Psoriasis patients' peripheral blood mononuclear cells (PBMCs) had elevated levels of IL-38 mRNA, which was associated with a more severe case of the illness, according to the research. According to another study (33), it has been suggested that IL-38 expression could be induced as a counter-regulatory mechanism to balance inflammatory responses in psoriasis by stimulating primary PBMCs and human keratinocytes with IL-17A, TNF-α, and interferon-γ.

Researchers have looked at IL-38 expression in a number of autoimmune and inflammatory disorders. Levels of IL-38, which correlate with disease severity and inflammatory indicators including total immunoglobulin E and eosinophilic count, were shown to be substantially greater in atopic dermatitis patients compared to healthy controls in one research (34). An additional research indicated that individuals with systemic lupus erythematosus (SLE) had higher levels of IL-38, which was associated with disease activity and severe clinical symptoms such lupus nephritis and involvement of the central nervous system (35).

A similar pattern was seen in rheumatoid arthritis patients, where elevated levels of IL-38 serum protein and mRNA were associated with disease activity (37), and in patients newly diagnosed with systemic sclerosis and those not receiving therapy, elevated levels of IL-38 were also observed (36). Patients with primary Sjogren's syndrome also had elevated IL-38 levels in their labial salivary glands, which might be an immune system response to the overexpression of IL-36 and IL-17 that contribute to illness progression (38).

Vitiligo, which has genetic risk loci with atopic dermatitis, SLE, systemic sclerosis, RA, and Sjogren's disease, is one of the inflammatory and autoimmune disorders highlighted by these research as IL-38 plays an important role (39, 40). For vitiligo and similar disorders, this points to IL-38's possible importance as a biomarker and medicine target.

This research should be recognized for a number of shortcomings. The sample size was enough for discovering statistically significant differences, but it couldn't be used to draw conclusions about larger groups. Although IL-38 was the primary focus of this investigation, no additional anti-inflammatory cytokines that may have important roles in the development of vitiligo were investigated. The research only looked at one treatment method (NB-UVB). To confirm IL-38's function as a biomarker in vitiligo across other demographic groups, larger, multicenter investigations are required. To completely understand the inflammatory profile in vitiligo, future research should incorporate a wider variety of cytokines.

Conclusion

The present research shows that IL-38 is associated with disease activity and severity in vitiligo patients and is much higher in these individuals. Patients' VASI scores show a considerable improvement when compared to their pre- and post-treatment levels. All things considered, IL-38 shows promise as a biomarker

for monitoring vitiligo disease progression and treatment efficacy. The correlation between IL-38 levels and the intensity of vitiligo symptoms suggests that it may have a role in the disease's etiology, maybe as an anti-inflammatory counter-regulatory mechanism.

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