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Serum Interleukin-15 in Egyptian Vitiligo Patients

Aliaa Mohamed Eladl, Mohamed Khalid Galal, Yousra Ibrahim El-tantawy, Mohamed Hussein Elmogy
Department of Dermatology, Andrology & STDs, Faculty of Medicine, Mansoura University, Egypt
***Corresponding author:** Aliaa Mohamed Eladl**, Mobile:** (+20) 01027244597, **E-Mail:** aliaaeladl@icloud.com

ABSTRACT

Background: Vitiligo is a multifactorial acquired depigmenting skin disorder with poorly understood etiology. It is characterized by white macules and patches due to loss of functioning epidermal melanocytes. The most widely accepted hypothesis is the autoimmune-mediated melanocyte destruction through the interplay between cellular immunity, humoral immunity, and cytokine action. Peri-lesional vitiligo skin biopsies revealed CD8+ cytotoxic T (cT) cell infiltration proposing a cytotoxic attack against melanocytes. It has been hypothesized that IL-15 might play a role in this autoimmune disease; thus, inhibiting IL-15 activity might be a breaking new therapeutic strategy in the treatment of vitiligo.

Objective: The current study was conducted to assess the serum level of IL-15 in patients with non-segmental vitiligo, and to correlate its levels with disease duration, extent, and activity.

Patients and methods: The present study was a case-control study conducted on three groups of subjects attending the Dermatology Outpatient Clinic in Mansoura University Hospitals: 30 patients suffering from active non-segmental vitiligo, 30 patients with stable non-segmental vitiligo, and 30 age- and sex-matched healthy controls.

Results: Healthy controls and vitiligo cases demonstrated insignificant differences in terms of the demographic characteristics as well as the risk factors. IL-15 level demonstrated insignificant correlation with the gender, smoking, stress, and clinical type in both vitiligo groups. Higher IL-15 level was suggested to be independent risk predictor for vitiligo occurrence and severity but not activity.

Conclusion: It could be concluded that, vitiligo cases were associated with a significant elevation in IL-15 level.

Keywords: Vitiligo Extent Score, Cytotoxic T, Radioimmunoassay, Superoxide dismutase, Enzyme-linked immunosorbent assay

INTRODUCTION

Vitiligo is an acquired depigmenting skin disorder that affects 0.5–1% of the population worldwide and characterized by white macules and patches due to loss of functioning epidermal melanocytes [(1)]. Vitiligo has been classified into segmental vitiligo, non-segmental vitiligo (Acrofacial, Mucosal > 1 site, Generalized, Universal, Mixed), and undetermined / unclassified vitiligo (Focal, Mucosal, <1 site) [(2)]. Vitiligo is a multifactorial disease with poorly understood etiology. There are three major hypotheses for the pathogenesis of vitiligo; autoimmune, neural and biochemical (autocytotoxic) hypothesis [(3, 4)]. Today the autoimmune pathogenesis of the disease has become a rapidly evolving field of research. An autoimmune etiology is supported by the frequent association of vitiligo with autoimmune diseases and presence of autoantibodies and autoreactive T cells against melanocyte antigens [(5, 6)].

Many of the functions of immune cells are mediated through cytokines, and several studies have analyzed the presence of these molecules in vitiligo patients [(7, 8)]. Cytokines, which are pivotal in maintaining immune homeostasis, are crucial in vitiligo pathogenesis; and several studies indicate that there is an imbalance between pro- and anti-inflammatory cytokines in the skin and serum of vitiligo patients [(9)]. One of these cytokines, interlukin-15 (IL-15), is a proinflammatory cytokine and its expression is upregulated under inflammatory conditions [(10)].

Interlukin-15 is a pleiotropic cytokine that plays an important role in both the innate and adaptive immune system and was found to be a critical factor for the development & proliferation of $CD8^+$ memory T cells [(11, 12)]**.** The aim of this study was to assess the serum level of IL-15 in patients with non-segmental vitiligo; and to correlate its levels with disease duration, extent, and activity.

PATIENTS AND METHODS

This case-control study included a total of 60 patients suffering from vitiligo and 30 age-matched healthy controls, attending at Dermatology Outpatient Clinic, Mansoura University Hospitals.

The included subjects were divided into three groups; **Group 1** consisted of 30 patients suffering from active non-segmental vitiligo (active vitiligo means patients reporting worsening of already existent lesions as well as the development of new lesions during the previous 3 months), **Group 2** consisted of 30 patients with stable non-segmental vitiligo, and **Group 3 (control)** consisted of 30 age-matched healthy controls of both genders without previous, or current, or any family history for vitiligo nor autoimmune diseases.

Inclusion criteria

Patients with active and stable non-segmental vitiligo receiving no treatment for vitiligo in the past 1 month.

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Exclusion criteria

Patients with segmental or unclassified vitiligo. Healthy controls had personal or family history of vitiligo. Subjects with accompanying comorbidities, particularly autoimmune diseases and subjects who received any treatment for vitiligo in the past 1 month.

All patients were subjected to:

1. Complete history taking: Full personal, family and present history of vitiligo (onset, course, duration and previous treatment).
2. General examination.
3. Dermatological examination.
4. Estimation of the affected body surface area using Vitiligo Extent Score (VES) [13].
5. Laboratory investigation: Serum levels of IL-15 were measured using ELISA kits (QUANTA Lite® ELISA, INOVA Diagnostic, Inc) using serum samples from patients with vitiligo and healthy controls (frozen at -80º C until assayed).

Human IL-15 (Interleukin 15) ELISA Kit:
Kits components of human interleukin -15:

Kit Components No.	Item	Specifications (48T/96T)	Storage
E001	ELISA Microplate (Dismountable)	8×6/8×12	2-8°C/-20°C
E002	Lyophilized Standard	1vial/2vial	2-8°C/-20°C
E039	Sample/Standard Dilution Buffer	10ml/20ml	2-8°C
E003	Biotin-labeled Antibody (Concentrated)	60ul/120ul	2-8°C (Avoid Direct Light)
E040	Antibody Dilution Buffer	5ml/10ml	2-8°C
E034	HRP-Streptavidin Conjugate (SABC)	60ul/120ul	2-8°C (Avoid Direct Light)
E049	SABC Dilution Buffer	5ml/10ml	2-8°C
E024	TMB Substrate	5ml/10ml	2-8°C (Avoid Direct Light)
E026	Stop Solution	5ml/10ml	2-8°C
E038	Wash Buffer (25X)	15ml/30ml	2-8°C
E006	Plate Sealer	3/5pieces	
E007	Product Description	1copy	

Ethical considerations:

An approval of the study was obtained from Mansoura University academic and ethical committee. Every patient signed an informed written consent for acceptance of the operation. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The collected data was revised, coded, tabulated, and introduced to a PC using Statistical package for Social Science (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Data were presented and suitable analysis was done according to the type of data obtained for each parameter. Shapiro test was done to test the normality of data distribution. Mean, Standard deviation (± SD) for parametric numerical data, while Median and range for non-parametric numerical data. Frequency and percentage of non-numerical data.

Student T Test was used to assess the statistical significance of the difference between two study group means. **For the comparison of the three groups'** means, one way analysis of variance (ANOVA) was used. **Mann Whitney Test (U test)** was used to assess the statistical significance of the difference of a non-parametric variable between two study groups.

The Kruskal-Wallis test was used to assess the statistical significance of the difference between more than two study group nonparametric variables. The ROC Curve (receiver operating characteristic) provides a useful way to evaluate the sensitivity and specificity for quantitative diagnostic measures that categorize cases into one of two groups. The optimum cut off point was defined as that which maximized the AUC value. AUC is that a test with an area greater than 0.9 has high accuracy, while 0.7–0.9 indicates moderate accuracy, 0.5–0.7, low accuracy and 0.5 a chance result. Logistic and linear regression analyses were used for prediction of risk factors, using generalized linear models. Odds ratio and 95% confidence interval were calculated. A p value is considered significant if <0.05 at confidence interval 95%.

RESULTS

This study was conducted on 3 groups: 30 patients suffering from active non-segmental vitiligo, 30 patients with stable non-segmental vitiligo and 30 age- and sex-matched healthy controls. The mean age of patients with stable vitiligo, patients with active vitiligo, and control group was 36.2 years, 35.4 years, and 36.6 years, respectively. Both stable and active groups comprised 10 males (33.3 %) and 20 females (66.7 %). No significant intergroup difference was detected between the mean value for age or sex (p= 0.759 and 0.750, respectively) (Table 1).

Table (1): Demographic characteristics of studied groups:

		Controls N=30	Vitiligo			P^1	P^2
			Total N=60	**Stable N=30**	**Active N=30**		
Age (years)	**Mean ±SD**	36.6 ±11.2	35.8 ±10.8	36.2 ±10.9	35.4 ±10.9	0.759	0.786
Males	**N**	9	20	10	10	0.750	1
	%	30%	33.3%	33.3%	33.3%		
Females	**N**	21	40	20	20		
	%	70%	66.7%	66.7%	66.7%		
SD, standard deviation; student *t* test was used for numerical parameters; Chi square test was used for categorical parameters; *p*1, comparison between all studied cases and control groups; *p*2, comparison between stable and active vitiligo cases.							

The mean age at onset did not differ significantly between active and stable cases (P> 0.05). Median disease duration among all studied cases was 2 months (ranged from 2 weeks to 1 year); and the median VES score was 2.5 (ranged from 0.11 to 30.5) in all studied cases (Table 3). No significant differences were found between active and stable cases regarding disease duration and VES score. The commonest type of vitiligo among all cases was the generalized (48.3 %) followed by the acrofacial type (36.7%). There was no significant difference in the incidence of vitiligo type (P= 0.204) between active and stable cases. The generalized type was the commonest among active (53.3 %) and stable (43.3 %) cases, followed by the acrofacial vitiligo (33.3 % in active cases and 40 % in stable cases). The least common type was the mucosal type that was observed in 2 active vitiligo cases only (6.7 %) (Table 2).

Table (2): Clinical features in all studied vitiligo cases

			Vitiligo			
			Total N=60	**Stable N=30**	**Active N=30**	***p***
Age at onset (years)		**Mean ± SD**	35.6 ± 10.8	35.9 ± 10.9	35.2 ± 10.9	0.812
Disease duration (months)		**Median (range)**	2 (0.5 - 12)	2.5 (0.5 - 12)	2 (1 – 7)	0.345
VES		**Median (range)**	2.5 (0.11-30.5)	1.6 (0.1- 9.7)	2.9 (0.3-30.5)	0.307
Clinical Type	**Generalized**	**N (%)**	29 (48.3 %)	13 (43.3 %)	16 (53.3 %)	0.204
	Acrofacial	**N (%)**	22 (36.7 %)	12 (40.0 %)	10 (33.3 %)	
	Focal	**N (%)**	7 (11.7 %)	5 (16.7 %)	2 (6.7 %)	
	Mucosal	**N (%)**	2 (3.3 %)	0 (0.0 %)	2 (6.7 %)	
SD, standard deviation; student t test was used for comparison of onset; Mann Whitney U test was used for comparison of duration and VES; Chi square test was used for comparison of categorical parameters; p, comparison between stable and active vitiligo cases.						

Table (3) shows that IL-15 was significantly higher in vitiligo cases (72.1 pg/ml) when compared to control group (13.9 pg/ml), and the difference was statistically significant (p< 0.001). Serum levels of IL-15 was higher (84.9 pg/ml) in active vitiligo cases when compared to the stable group (72.1 pg/ml) but the difference was statistically non-significant (p< 0.104).

Table (3): Comparison of median IL-15 levels between cases and control groups

		Control N=30	Vitiligo			P^1	P^2
			Total N=60	**Stable N=30**	**Active N=30**		
IL-15 (pg/ml)	**Median**	13.9	72.1	72.1	84.9	<0.001	0.104
Man Whitney U test was used for comparison of numerical parameters; p1, comparison between all studied cases and control groups; p2, comparison between stable and active vitiligo cases.							

Receiver operating characteristic (ROC) curve of IL-15 was conducted to evaluate the sensitivity and specificity of serum IL-15 as a diagnostic index for vitiligo. IL-15 showed high accuracy AUC (AUC= 0.937); there was a statistically significant diagnostic value compared with the AUC/ROC value of 0.5 (P< 0.001). At best cut off value of 18.5 pg/ml, sensitivity was 98.3%, specificity was 83.3%, PPV was 98.3%, NPV was 83.3%, and accuracy was 93.3% (Table 4).

Table (4): Validity of IL-15 level for discrimination between vitiligo cases and control groups:

	IL-15
AUC	0.937
Cut off (pg/mL)	≥ 18.5
Sensitivity (%)	98.3
Specificity (%)	83.3
PPV (%)	98.3
NPV (%)	83.3
Accuracy (%)	93.3
AUC: area under curve; PPV: positive predictive value; NPV: negative predictive value.	

ROC curve of IL-15 levels was conducted to evaluate the sensitivity and specificity of serum IL-15 as a diagnostic index for discrimination between stable and active vitiligo cases. The AUC-ROC of IL-15 was low (AUC=0.622). At best cut off value of 65.6, sensitivity was 60%, specificity was 43.3%, PPV was 60%, NPV was 43.3%, and accuracy was 51.7% (Table 5).

Table (5): Validity of IL-15 level for discrimination between stable and active vitiligo cases:

	IL-15
AUC	0.622
Cut off (pg/mL)	65.6
Sensitivity (%)	60
Specificity (%)	43.3
PPV (%)	60
NPV (%)	43.3
Accuracy (%)	51.7

AUC, area under ROC, OC, receiver operating curve; PPV, positive predictive value; NPV, negative predictive value.

Linear regression analysis was conducted for prediction of vitiligo severity (higher VES score) using age, gender, smoking, stress, onset, duration and IL-15 levels as covariates. Higher IL-15 level was considered as independent predictor of vitiligo severity (Table 6).

Table (6): Regression analysis for prediction of factors affecting severity of vitiligo (higher VES score)

	β	*p*
Age	-0.007	0.916
Gender	2.445	0.175
Smoking	1.717	0.282
Stress	1.335	0.340
Onset	-0.007	0.908
Duration	0.124	0.638
IL-15	0.093	**<0.001**
***β*, linear regression coefficient.**		

DISCUSSION

Vitiligo is an acquired depigmenting skin disorder that affects 0.5-1% of the population worldwide. It is characterized by white macules and patches due to loss of functioning epidermal melanocytes [(1)]. Vitiligo is a multifactorial disease with poorly understood etiology. Its pathogenesis remains unclear and is thought to be triggered by various etiological factors that eventually contribute to melanocytes destruction. There are three major hypotheses for the pathogenesis of vitiligo; autoimmune, neural and biochemical (auto-cytotoxic) hypotheses [(3, 4)].

Today, the autoimmune pathogenesis of the disease has become a rapidly evolving field of research. An autoimmune etiology is supported by the frequent association of vitiligo with autoimmune diseases and presence of autoantibodies and autoreactive T cells against melanocyte antigens [(6)].

The most widely accepted hypothesis is the autoimmune-mediated melanocyte destruction through the interplay between cellular immunity, humoral immunity, and cytokine action. Peri-lesional vitiligo skin biopsies revealed CD8+ cytotoxic T (cT) cell infiltration proposing a cytotoxic attack against melanocytes. In addition, an elevated expression of tumor necrosis factor (TNF)-α and interferon (INF)-γ was detected, suggesting a Th1 cell response [(9)]. Many of the functions of the immune cells are mediated through cytokines, and several studies have analyzed the presence of these cytokines in vitiligo patients [(9)]. One of these cytokines, IL-15, is a pro-inflammatory cytokine and its expression is up-regulated under inflammatory conditions. Interlukin-15 is a pleiotropic cytokine that plays an important role in both the innate and adaptive immune system; and was found to be a critical factor for the development and proliferation of CD8+ memory T cells. It has been hypothesized that IL-15 might play a role in this autoimmune disease; thus, inhibiting IL-15 activity might be a breaking new therapeutic strategy in the treatment of vitiligo[(11)].

The current study was conducted to assess the serum level of IL-15 in patients with non-segmental vitiligo, and to correlate its levels with disease duration, extent, and activity.

The present study was a case-control study conducted on three groups of subjects: 30 patients suffering from active non-segmental vitiligo, 30 patients with stable non-segmental vitiligo, and 30 age- and sex-matched healthy controls. Concerning demographic data among vitiligo groups, no significant difference was detected. No significant differences were also found regarding smoking and stress among the studied groups.

The current results demonstrated that the mean age at onset of the disease did not differ significantly between active and stable cases. The median disease duration among all studied cases was two months and

the median VES score was 2.5 in all studied cases. Accordingly, no significant differences were found between active and stable cases regarding disease duration and VES score. Concerning the different common types of vitiligo among the studied groups, the present work revealed that the commonest type of vitiligo among all cases was the generalized type (48.3%), followed by the acrofacial type (36.7%). There was no significant difference in the incidence of vitiligo type between active and stable cases. The generalized type was the commonest among active (53.3%) and stable (43.3%) cases, followed by the acrofacial vitiligo (33.3% in active cases and 40% in stable cases). The least common type was the mucosal type that was observed in two active vitiligo cases only (6.7%).

Regarding the serum levels of IL-15 in the studied groups, the current results showed that IL-15 was significantly higher in vitiligo cases (72.1 pg/ml), when compared to control group (13.9 pg/ml), and the difference was statistically significant between both groups. Serum levels of IL-15 was higher (84.9 pg/ml) in active vitiligo cases, when compared to the stable group (72.1 pg/ml), but there was statistically non-significant difference between the studied groups. In addition, the present work demonstrated a positive correlation between serum IL-15 level and VES in vitiligo cases, which was statistically significant. Moreover, serum IL-15 level showed a significant positive correlation with VES score in stable and active vitiligo groups. However, no significant correlation was found between serum IL-15 level and age, onset, or duration in all studied cases, as well as in the active vitiligo cases.

It has been proved that IL-15 can stimulate neighbor cells through a trans-presentation mechanism that involves the secretion of IL-15 and IL-15Rα complexes from the surface of DCs or monocytes into endosomes to be presented in trans to neighboring cT cells or NK cells. Several studies have postulated that IL-15 can promote survival and maturation of NK cells, neutrophils, and DCs [(14)]. Furthermore, IL-15 can potentiate NK cell cytotoxicity and cytokine production like IFN-γ and TNF-α as well as the phagocytic activity of macrophages and neutrophils. In addition, DCs efficiently regulate the development and survival of memory cT cells by IL-15 trans-presentation. Moreover, it has been found that IL-15 has a role in enhancing the T-cell receptor-dependent proliferation of Th17 [(15)].

Interleukin-15 has been shown to play a crucial function in the pathogenesis of different autoimmune diseases, such as inflammatory bowel disease, rheumatoid arthritis, systemic sclerosis, psoriasis and alopecia areata [(15-17)]. Antagonizing IL-15 by antibodies targeting IL-15 or IL-15Rβ chain and mutant IL-15/Fc fusion protein has been suggested as a promising therapeutic strategy for these diseases [(18)].

In accordance with the current results was the recent study aiming at evaluating IL-15 level in the sera of patients with vitiligo and its association with vitiligo severity and activity. That study included 30 patients with non-segmental vitiligo, and 30 healthy controls. Vitiligo Extent Score (VES) and Vitiligo Disease Activity (VIDA) score were used to assess vitiligo severity and activity, respectively, and serum level of IL-15 was assessed by ELIZA. Results of that study revealed that serum IL-15 level, in patients with vitiligo, was significantly higher in comparison with the control group (P=0.001). Also, a significant positive correlation was found between serum IL-15 level and VES score (P=0.001), whereas there was no significant correlation between IL-15 level and VIDA score as well as the disease duration [(19)].

Similarly, these findings are in accordance with the aforementioned role of IL-15 on recruitment of cT cells, enhancing their cytotoxicity and promoting maturation and survival of memory cT cells. Interestingly, resident memory CXCR3+ melanocyte-specific cT cells were identified in the skin of stable and active vitiligo. Their continued presence in stable disease supported their role in disease flares. These cells express CD122 (IL-15Rβ), and it was postulated that IL-15 bound to CD215 (IL-15Rα) on keratinocytes can be trans-presented to them through CD122 [(20, 21)].

In agreement with our results, **Chen and his colleagues** demonstrated that the expression of IL-15 was significantly up-regulated in the epidermis of patients with vitiligo, produced mainly by keratinocytes, and was strongly associated with the load of epidermal H_2O_2 oxidative stress. In addition, the oxidative stress stimulated IL-15 and IL-15Rα expression on keratinocytes and also their trans-presentation of IL-15 enhancing the survival of resident memory cT cells [(22)]. In the same manner, IL-15 overexpression was found in several inflammatory and immune-mediated skin disorders. **Ebrahim *et al.*** [(15)] demonstrated that the serum level of IL-15 was increased significantly among patients with alopecia areata than in control subjects. Moreover, this level was positively associated with the disease severity, and hence, they concluded that IL-15 could be a potential predictor of alopecia areata severity. A study by **Rückert *et al.*** [(23)] has revealed increased expression of IL-15 in lesional skin of patients with psoriasis than in control subjects.

Recently, IL-15 and IL-23 have been shown to have an additional effect on the enhancement of Th 17 cytokines in psoriasis [(24)]**.** In addition, **Su *et al.*** [(25)] have showed that IL-15 was overexpressed in patients with Stevens-Johnson syndrome and toxic epidermal necrolysis, and its level was positively correlated with disease severity and mortality [(25)]. Moreover, **Karlen *et al.*** [(26)] found a significantly higher expression of IL-15 in lesional and non-lesional skin of patients with atopic dermatitis compared with healthy controls.

In the current study, the Receiver operating characteristic (ROC) curve of IL-15 was conducted to evaluate the sensitivity and specificity of serum IL-15 as a diagnostic index for vitiligo. IL-15 showed high accuracy AUC (AUC= 0.937); there was a statistically

significant diagnostic value compared with the AUC/ROC value of 0.5. At best cut off value of 18.5 pg/ml, sensitivity was 98.3%, specificity was 83.3%, PPV was 98.3%, NPV was 83.3%, and accuracy was 93.3%. In addition, ROC curve of IL-15 levels was conducted to evaluate the sensitivity and specificity of serum IL-15 as a diagnostic index for discrimination between stable and active vitiligo cases. The AUC-ROC of IL-15 was low (AUC=0.622). At best cut off value of 65.6, sensitivity was 60%, specificity was 43.3%, PPV was 60%, NPV was 43.3%, and accuracy was 51.7%. Moreover, linear regression analysis was conducted for prediction of vitiligo severity (higher VES score) using age, gender, smoking, stress, onset, duration, and IL-15 levels as covariates. Higher IL-15 level was considered as independent predictor of vitiligo severity.

CONCLUSION

The current study has demonstrated that, vitiligo cases were associated with a significant elevation in IL-15 level. Additionally, it was demonstrated to be correlated positively with VES. Thus, IL-15 level could be used a reliable marker for the development of vitiligo as well as it severity.

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REFERENCES

1. **Alikhan A, Felsten L, Daly M *et al.* (2011):** Vitiligo: a comprehensive overview: part I. Introduction, epidemiology, quality of life, diagnosis, differential diagnosis, associations, histopathology, etiology, and work-up. Journal of the American Academy of Dermatology, 65(3):473-91.
2. **Ezzedine K, Lim H, Suzuki T *et al.* (2012):** Revised classification/nomenclature of vitiligo and related issues: the Vitiligo Global Issues Consensus Conference. Pigment Cell & Melanoma Research, 25(3): 1-13.
3. **Pawelek J, Körner A, Bergstrom A *et al.* (1980):** New regulators of melanin biosynthesis and the autodestruction of melanoma cells. Nature, 286(5773):617-9.
4. **Ongenae K, Van Geel N, Naeyaert J (2003):** Evidence for an autoimmune pathogenesis of vitiligo. Pigment Cell Research, 16(2):90-100.
5. **Naughton G, Eisinger M, Bystryn J (1983):** Antibodies to normal human melanocytes in vitiligo. The Journal of Experimental Medicine, 158(1):246-51.
6. **Shahid S, Ahmad Reza T, Zari J *et al.* (2014):** Association between vitiligo and diabetes mellitus: a case control study. Iranian Journal of Dermatology, 17(1):22-6.
7. **Caixia T, Hongwen F, Xiran L (1999):** Levels of soluble interleukin-2 receptor in the sera and skin tissue fluids of patients with vitiligo. Journal of Dermatological Science, 21(1):59-62.
8. **Yu H, Chang K, Yu C *et al.* (1997):** Alterations in IL-6, IL-8, GM-CSF. TNF-α, and IFN-γ release by peripheral mononuclear cells in patients with active vitiligo. Journal of Investigative Dermatology, 108(4):527-9.
9. **Singh M, Kotnis A, Jadeja S *et al.* (2019):** Cytokines: the yin and yang of vitiligo pathogenesis. Expert review of Clinical Immunology, 15(2):177-88.
10. **Fehniger T, Caligiuri M (2001):** Interleukin 15: biology and relevance to human disease. Blood, The Journal of the American Society of Hematology, 97(1):14-32.
11. **Vijay N, Lijo J, Dechamma H *et al.* (2015):** Expression of bovine interleukin 15 and evaluation of its biological activity in vitro. Veterinary World, 8(3):295-99.
12. **Diab A, Cohen A, Alpdogan O *et al.* (2005):** IL-15: targeting CD8+ T cells for immunotherapy. Cytotherapy, 7(1):23-35.
13. **van Geel N, Lommerts J, Bekkenk M *et al.* (2016):** Development and validation of the Vitiligo Extent Score (VES): an international collaborative initiative. Journal of Investigative Dermatology, 136(5):978-84.
14. **Stonier S, Schluns K (2010):** Trans-presentation: a novel mechanism regulating IL-15 delivery and responses. Immunology Letters, 127(2):85-92.
15. **Ebrahim A, Salem R, El Fallah A *et al.* (2019):** Serum interleukin-15 is a marker of alopecia areata severity. International Journal of Trichology, 11(1):26-30.
16. **Di Sabatino A, Calarota S, Vidali F *et al.* (2011):** Role of IL-15 in immune-mediated and infectious diseases. Cytokine & Growth Factor Reviews, 22(1):19-33.
17. **Machado Diaz A, Capote A, Arrieta Aguero C *et al.* (2012):** Proinflammatory soluble interleukin-15 receptor alpha is increased in rheumatoid arthritis. Arthritis, 12: 335-339..
18. **Meghnem D, Morisseau S, Frutoso M *et al.* (2017):** Cutting edge: Differential fine-tuning of IL-2–and IL-15–dependent functions by targeting their common IL-2/15Rβ/γc receptor. The Journal of Immunology, 198(12):4563-8.
19. **Atwa M, Ali S, Youssef N *et al.* (2020):** Elevated serum level of interleukin-15 in vitiligo patients and its correlation with disease severity but not activity. Journal of Cosmetic Dermatology, 20: 183-187.
20. **Boniface K, Jacquemin C, Darrigade A *et al.* (2018):** Vitiligo skin is imprinted with resident memory CD8 T cells expressing CXCR3. Journal of Investigative Dermatology, 138(2):355-64.
21. **Richmond J, Strassner J, Zapata L *et al.* (2018):** Antibody blockade of IL-15 signaling has the potential to durably reverse vitiligo. Science Translational Medicine, 10(450): 95-101.
22. **Chen X, Guo W, Chang Y *et al.* (2019):** Oxidative stress-induced IL-15 trans-presentation in keratinocytes contributes to CD8+ T cells activation via JAK-STAT pathway in vitiligo. Free Radical Biology and Medicine, 139:80-91.
23. **Rückert R, Asadullah K, Seifert M *et al.* (2000):** Inhibition of keratinocyte apoptosis by IL-15: a new parameter in the pathogenesis of psoriasis? The Journal of Immunology, 165(4):2240-50.
24. **de Jesús-Gil C, Ruiz-Romeu E, Ferran M *et al.* (2020):** IL-15 and IL-23 synergize to trigger Th17 response by CLA+ T cells in psoriasis. Experimental Dermatology, 29(7):630-8.
25. **Su S, Mockenhaupt M, Wolkenstein P *et al.* (2017):** Interleukin-15 is associated with severity and mortality in Stevens-Johnson syndrome/toxic epidermal necrolysis. Journal of Investigative Dermatology, 137(5):1065-73.
26. **Karlen H, Yousefi S, Simon H *et al.* (2020):** IL-15 expression pattern in atopic dermatitis. International Archives of Allergy and Immunology, 181(6):417-21.