Serum CCL20 Level in Patients with Vitiligo

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ABSTRACT

Background: Vitiligo is a chronic, acquired depigmenting cutaneous disorder due to damage of melanocytes in genetically susceptible persons. The existence of vitiligo is mediated by the autoimmune dysfunction of cases. CCL20 was expressed at low levels in normal human skin, because both CCL20 and CCR6 were significantly up-regulated within chronic inflammatory cutaneous disorders.CCL20 interacts with its receptor CCR6 to recruit IL-17A-forming cells into skin.

Objective: This study was aimed to assess relationship between serum level of CCL20 in cases with vitiligo and its correlation to disease severity and activity

Patients and methods: This case-control study included a total of fifty cases with vitiligo and 30 matched age and sex control attending at the outpatient clinic of Dermatology, Mansoura University Hospital.

Results: CCL20 levels were considerably greater within vitiligo cases when compared to controls. CCL20 levels were found to be considerably higher in active vitiligo cases in comparison to stable vitiligo cases.

Conclusion: It could be concluded that the serum level of CCL20 was demonstrated to be correlated positively with vitiligo-affected patients. Additionally, it seems to have a positive association with disease activity but not with disorder duration so CCL20 could be a candidate as a biomarker to evaluate the activity of vitiligo as well as it is a good predictor of vitiligo and discriminates patients from control.

Keywords: vitiligo, CCL20, melanocytes, VETF, skin.

INTRODUCTION

Vitiligo is a chronic, acquired depigmenting cutaneous disorder due to selective damage of melanocytes in genetically susceptible cases. It shows well-circumscribed, milky-white depigmented macules [(1)]**.** overall incidence is nearly 1%, with 80% of patients happening below 30 years influencing both sexes similarly [(2)]**.**

Vitiligo is a melanocyte-specific damage disease having complex pathogenesis. Although autoimmunity causing a melanocyte-specific response with adaptive immunity is currently considered as the main pathway, this theory alone does not explain the pathogenesis as a whole. Intrinsic defects within melanocytes including oxidative stress, melanocytorrhagy, neural mechanisms, adhesion defects, and inflammasomes are the other different mechanisms proposed to be involved in vitiligo lesions [(3)]**.** It is assumed that incidence of vitiligo is related to autoimmune dysfunction of cases [(4, 5)].

The psychological, social and financial burdens of vitiligo are great. Vitiligo affects about 100 million people universal. People in poor countries tolerate the impact, because of possibility for inappropriate diagnosis of the disease, poor reach to effective managements, and stigmatization and discrimination **[(6)].** The most commonly used treatment of vitiligo are local steroids and ultraviolet light [(7)].

CCL20 was expressed at low to very low levels within normal cutaneous tissue, as both CCL20 and CCR6 were markedly upregulated within chronic inflammatory cutaneous diseases[(8)] **.** CCL20 reacts with its receptor CCR6 to recruit IL-17A-forming cells into skin [(9)].

The aim of the current study was to assess relationship between serum level of CCL20 within cases with vitiligo and its correlation to disease severity and activity

PATIENTS AND METHODS

This case-control study included a total of 50 cases with vitiligo and 30 age and sex matched control attending at the Dermatology Outpatient Clinic, Mansoura University Hospital. This study was conducted between May 2019 till December 2020.

Inclusion criteria:
Age: from 20 to 70 years, both sexes with generalized, Focal, Acrofacial, and Mucosal vitiligo

Exclusion criteria: cases with history of autoimmune disorder that can affect IL17 level hence affect CCL20 level e.g. Thyroiditis and Psoriasis, Diabetes mellitus, Pernicious anemia, Atopic dermatitis, Inflammatory skin disorders with autoimmune background, Pregnant cases and those who on systemic treatment for 6 months before the study.

This study was carried out on two groups:
Group A (patient group): included 50 patients with vitiligo subdivided into 25 active vitiligo and 25 stable vitiligo**.**

Group B (control group): included 30 healthy persons who match the patients in the same age and sex.

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All participants were subjected to:

1) **Full history taking:** including age, duration of disorder, presence of any other family member with vitiligo, comorbidities, previous medical history, and current treatment.
2) **Full clinical examination**: By using wood s lamp Patients
   - **a.** Active vitiligo patients (25 cases)**:** Confetti-like macules and trichrome vitiligo are clinical signs of active vitiligo [10].
   - b. Stable vitiligo patients (25 cases)
   - c. Stable and active vitiligo are according to VETF score

3) Assessment of vitiligo by Vitiligo European Task Force (VETF)

VETF is a method which uses 3 features of vitiligo: extent, stage, and progress of disorder [11]. Extent depends on rule of nines [12]. Staging utilizes skin and hair pigmentation in vitiligo patches and categorized into 3 stages:

- **Stage 0:** Normal pigmentation.
- **Stage 1:** Partial depigmentation.
- **Stage 2:** Whole depigmentation (hair whitening <30%.
- **Stage 3:** Whole depigmentation + hair whitening <30% .

"Spreading" in VETF is (+1: progressive; 0: stable; −1: regressive [13].

Active vitiligo is characterized by VETF score of +1 to +5, or showed novel pathologies or progression within six months.

Stable vitiligo is characterized by VETF score of −5 to −1, and patients' self-reporting of no progression nor novel pathologies within six months [10].

The extent is assessed via 'rule of nines,' that supposes that every of the following zones encompasses 9% of the body surface area: head/neck; every arm; every leg; chest; abdomen; upper back; and lower back. The residual 1% is for genital organ [13] .

Staging depends upon extent of depigmentation and hair whitening. This evaluation is graded on scale from 0 to 4 on the largest macule within every body zone, excluding hands and feet, that are evaluated separately as single unique zone. evaluation of spreading depends upon Wood's lamp assesment of the largest macule within every zone on a scale from +1 to –1 (+1 = progressive; 0 = stable; –1 = regressive) [14].

4) Laboratory investigations:

Serum CCL20 was estimated via ELISA kits (Sunredbio, Catalogue No. 201-12-0087), consistent with manufacturer's instructions with a least detection limit of 0.5 pg/ml and the greatest detection limit of 150 pg/ml [15] .

Ethical consent:

The research approval of the study was got from IRB of Faculty of Medicine at Mansoura University prior beginning the research. Number of ethical approval is 19.05.616. The researcher elucidated the objective and aim of the study to the subjects involved within study. The researcher guaranteed keeping anonymity and confidentiality of the subject's data. Subjects were told that they were allowable to choose to share or not in the research and that, they had the right to leave the research at any time without explaining causes. This study was performed according to Code of Ethics of the World Medical Association (Declaration of Helsinki) for researches including humans.

Statistical analysis

Data were analyzed by IBM SPSS software package version 20.0**. (**Armonk, NY: IBM Corp**)** categorical data were expressed as numbers and percent. normality of distribution was tested via **K-S test**. Quantitative data were described using (minimum and maximum, mean, standard deviation, median, and IQR. **P < 0.05** was regarded to become statistically significant.

Chi-square test was used for categorical data, to compare among various groups**. Student t-test** was utilized for normally distributed quantitative variables, to compare among two studied groups**.**

Mann Whitney test was used for abnormally distributed quantitative variables, to compare among the two studied groups**. Spearman coefficient** was utilized to associate among two distributed abnormally quantitative data. **Kruskal Wallis test** was used for abnormally distributed quantitative variables, to compare among more than 2 studied groups**. Receiver operating characteristic curve (ROC)** is formed via plotting sensitivity (TP) on Y axis versus 1-specificity (FP) on X axis at various cut off values. The area under the ROC curve represents diagnostic performance of the test. Area >50% is regarded satisfactory performance and area near 100% is the best performance for the test. ROC curve permits comparison of performance among 2 tests.

RESULTS

The present study included 50 cases with vitiligo and 30 matched age and sex control attending the outpatient clinic of Dermatology, Mansoura University Hospital -Egypt

This research involved 2 groups, patients group comprised 50 cases with vitiligo, 25 active vitiligo (50%), and 25 stable vitiligo (50%), and the control group involved 30 healthy, age and sex-matched persons.

Table (1): Comparison among the two studied groups upon demographic data**.**

	Group A (n = 50)		Group B (n = 30)		Test of Sig.	p
	No.	%	No.	%		
Sex						
Male	16	32.0	10	33.3	χ^2= 0.015	0.902
Female	34	68.0	20	66.7		
Age (years)						
Min. – Max.	20.0 – 50.0		20.0 – 53.0		t= 1.271	0.208
Mean ± SD.	30.26 ± 9.82		27.63 ± 8.39			
Median (IQR)	26.50(21.0 – 38.0)		25.0(22.0 – 30.0)			

As regards the age of patients and control groups. The mean age of cases was 30.26 ±9.82years, while the mean age of controls was 27.63 ± 8.39 years. There is a non-significant difference among the ages of both groups. Regarding sex of patients and control groups. The patient group involved 16 males (32%) and 34 females (68%), While the control group involved 10 males (33.3%) and 20 females (66.7%). There is a non-significant difference among sexes of both groups as shown in Table (1).

Table (2): Distribution of the included patients upon Activity, duration, family history in patients group (n = 50)

	No.	%
Activity		
Active vitiligo	25	50.0
Stable vitiligo	25	50.0
Duration(in years)		
Min. – Max.	0.33 – 35.0	
Mean ± SD.	7.67 ± 8.14	
Median (IQR)	5.0 (2.0 – 10.0)	
Family history		
No	45	90.0
Yes	5	10.0

Table (2) illustrates that the mean disease duration of the study was 7.67 ± 8.14 years. There was a positive family history in 5 patients (10%).

Table (3): Descriptive analysis of the studied cases in relation to VETF score in patients group (n = 50)**.**

VETF score	Min. – Max.	Mean ± SD.	Median (IQR)
Area	1.00 – 67.00	12.26 ± 11.56	8.50(4.0 – 17.0)
Staging	1.00 – 15.00	5.80 ± 3.12	5.0 (4.0 – 8.0)
Spreading	-3.0 – 3.0	0.02 ± 1.57	0.0(-1.0 – 1.0)

As regard VETF score, the mean of the area affected by vitiligo was 12.26 ± 11.56 %, the mean of staging was 5.80 ± 3.12, the mean of spreading was 0.02 ± 1.57 as illustrated in Table (3)

Table (4): Distribution of the included cases along with treatment 6 months before blood Sampling in patients group (n = 50).

Treatment 6 months before bl. Sampling	No.	%
Topical	6	12.0
Photo Therapy	11	22.0
Photo Therapy & systemic	5	10.0
Topical & Photo Therapy	24	48.0
Topical & Photo Therapy & systemic	4	8.0

The most common type of treatment is 6 months before bl. sampling in patients group was Topical & Photo Therapy (48%) as shown in Table (4).

Table (5): Distribution of the included patients in consistent with type of vitiligo in patients group (n = 50)

Type of vitiligo	No.	%
Focal	6	12.0
Generalized	39	78.0
Acrofacial	4	8.0
Mucosal	1	2.0

Table (5) reveals that the commonest type of vitiligo was the generalized variety (78%).

Table (6): Distribution of the studied cases in consistent with site in patients group (n = 50).

Site	No.	%
Head & neck	33	66.0
Trunk	31	62.0
Hand & Feet	28	56.0
Leg	27	54.0
Arm	19	38.0
Genitalia	6	12.0

Table (6) illustrates that the most common site affected in the patient group was the Head & neck (66%).

Table (7): Comparison among two studied groups in relation to CCL20.

CCL20	Patient (n = 50)	Control (n = 30)	U	p
Mean ± SD.	94.02 ± 5.92	2.08 ± 0.08		
Median (IQR)	92.05	1.95		

Table (7) show that **CCL20** levels were showed to become considerably greater within vitiligo cases in comparison to controls (P<0.001).

Table (8): Association between activity and CCL20 within patients' group (n = 50).

CCL20 (pg/ml)	Activity		U	P
	Active (n = 25)	Stable (n = 25)		
Mean ± SD.	128.82 ± 9.24	59.22 ± 5.11		
Median	130.0	59.0		

Table (8) illustrates that CCL20 levels were showed to become considerably greater within active vitiligo cases in comparison to stable vitiligo patients (P<0.001).

Table (9): Correlation between CCL20 and VETF score and duration in patients' group (n = 50)

	CCL20	
	r_s	p
VETF score		
%area	0.778	<0.001*
Staging	0.702	<0.001*
Spreading	0.775	<0.001*
Duration	0.089	0.537

There was a significantly positive association between VETF score and CCL 20 levels. There was not a considerably positive correlation between duration of disease and CCL 20 levels as shown in Table (9).

Table (10): Relation between type of vitiligo and CCL20 in patients group (n = 50).

CCL20	Type of vitiligo				H	P
	Focal (n= 6)	Generalized (n= 39)	Acrofacial (n= 4)	Mucosal (n= 1#)		
Mean ± SD.	74.12 ± 3.43	101.96 ± 4.75	56.90 ± 1.65	52.40		
Median	55.50	118.10	56.80			

#: Excluded from the comparison due to small number of case (n = 1)

Table (10) illustrates that there was a significantly positive correlation between the type of vitiligo and CCL 20 levels.

Table (11): Relation between Treatment 6 months before bl. Sampling and CCL20 in cases group (n = 50).

CCL20	Treatment 6 months before bl. Sampling					H	P
	Topical (n= 6)	Photo Therapy (n= 11)	Photo Therapy & systemic (n= 5)	Topical & Photo Therapy (n= 24)	Topical & Photo Therapy & systemic (n= 4)		
Mean ± SD.	102.63 ± 4.91	82.23 ± 5.39	115.82 ± 3.45	89.10 ± 5.48	115.83 ± 38.08		
Median	117.65	61.0	126.0	64.45	132.15		

H: H for **Kruskal Wallis test**

Table (11) show that there was no positive correlation between Treatment 6 months before bl. Sampling and CCL20 levels.

Table (12): Validity (AUC, sensitivity, specificity) for CCL20 discriminate patients (n = 50) from control (n = 30).

	AUC	p	95% C.I	Cut off#	Sensitivity	Specificity	PPV	NPV
CCL20	1.000	<0.001*	1.0 – 1.0	>6.3	100.0	100.0	100.0	100.0

AUC: Area Under a Curve p value: Probability value CI: Confidence Intervals
NPV: Negative predictive value PPV: Positive predictive value
#Cut off was choose according to Youden index.

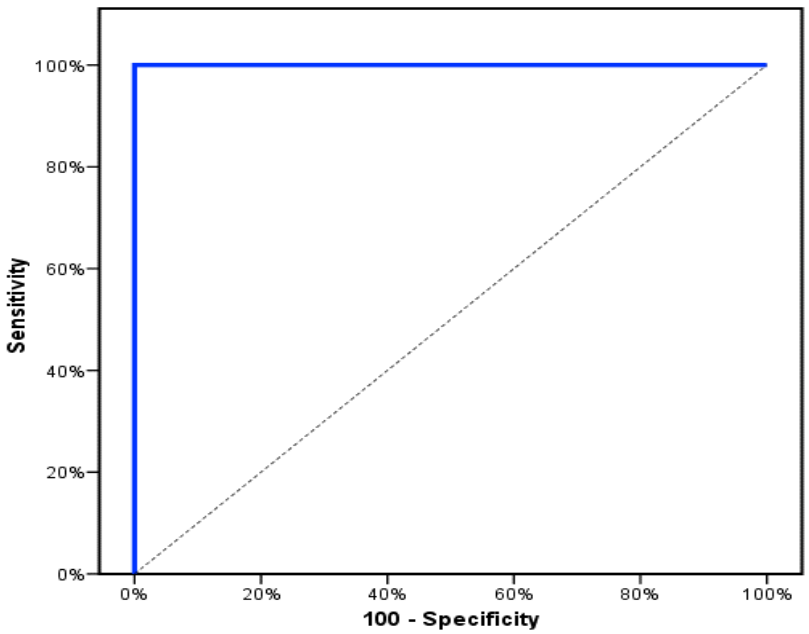

Figure (1): ROC curve for CCL20 discriminate patients (n = 50) from control (n = 30).

Table (12) and figure (1) reveals that the sensitivity and specificity of CCL 20 were evaluated using the (ROC). It was found that CCL20 showed a high significance in measuring the disease activity. Thus, we concluded that CCL20 could be a candidate as a biomarker to assess the activity of vitiligo. CCL20 is a good predictor of vitiligo and discriminates patients from control.

DISCUSSION

Vitiligo has an estimated incidence of 0.5–2% of the population. The disorder shows selective destruction of melanocytes that cause typical non-scaly, chalky-white macules and patches. although vitiligo is not a serious disorder, it is related to concomitant existence of several autoimmune disorders beside many psychosocial difficulties, considerably affecting the quality of life [16, 17]. Cytokines had mediate growth, differentiation, and control of immune cells, causing autoimmunity [18].

The current study was aimed to assess the relationship between levels of CCL20 in cases with vitiligo and its association to disease severity and activity.

To the best of our knowledge, there were very limited researches that discussed the role of CCL20 in vitiligo-affected subjects. The majority of previous researches were mainly emphasized other biomarkers including CXCL10, IL-17, and IL-27.

With regard to demographic features, the current study illustrated that the mean age of cases was 30.26 ±9.82years, while the mean age of controls was 27.63 ± 8.39 years. There wasn't any statistically significant difference among both groups regarding their demographic characteristics. Such fact indicated that both groups were comparable and such parameter (demographic characteristics) was not interfering with the net result of the study.

Similar age was recorded by **AL-Mousawi and his colleagues** [19]**;** who have demonstrated that the general mean of age of vitiligo groups was between 34.9 and 48.3. Unlike **Jain's study**, who found the mean of their ages was distributed between younger ages 20 and 40, incidence increased in the younger ages [20]. Another study found the age of patients ranged mostly in pediatric groups [21].

Concerning the distribution of the studied cases upon activity, duration, family history, the current research demonstrated that the mean disease duration of the studied was 7.67 ± 8.14 years. There was a positive family history in 5 patients (10%). Similarly **Zhang and his colleagues** have demonstrated that the mean vitiligo duration of active and stable cases were 5.51 ± 6.46 and 7.62 ± 6.23 respectively with no significant differences (P>0.05). In addition, positive family history was detected in five cases (5.8%) inactive vitiligo cases and in two cases (5%) in stable vitiligo cases [1].

As regards VETF score, our study showed that the mean of the area affected by vitiligo was 12.26 ± 11.56 %, the mean of staging was 5.80 ± 3.12 and the mean of spreading was 0.02 ± 1.57. While, **Zhang and his colleagues**; have demonstrated that 60 cases got active vitiligo, though 40 got stable vitiligo. Between the 60 cases with active vitiligo, twenty cases got VASI <5 and 40 patients had a VASI > 5 [1].

Concerning CCL20 in vitiligo-affected cases, the current study demonstrated that the CCL20 level was showed to become considerably greater in vitiligo cases in comparison with controls (P<0.001). In addition, CCL20 level was significantly higher in active vitiligo cases when compared to stable vitiligo patients (P<0.001). Moreover, there was a significantly positive association among VETF score and CCL 20 levels. However, there wasn't any significant positive association among duration of disorder and CCL20 levels. Such outcomes denoted that CCL20 is not only an indicator for vitiligo but also an indicator for vitiligo activity.This came in accordance with **AL-Mousawi and his colleagues;** who have demonstrated that CCL20 is significantly higher (P<0.05) among patients of active vitiligo in comparison to stable vitiligo ones, so positively correlated with disease activity. The sensitivity and specificity of the measured biomarker were evaluated using the (ROC). It was found that CCL20 showed a high significance in measuring the disease activity. Thus, they have concluded that CCL20 can become a candidate as marker to evaluate the activity of vitiligo [19].

In the same line, **Zhang and his colleagues;** have demonstrated that serum CCL20 level was considerably higher within cases with vitiligo. CCL20 was greater in active when compared to the stable stage that related positively with the VETF spreading score and VASI score. Cases with active vitiligo got numerous Th1/17 cells and Tc1/17 cells, and up-regulated expression of *CCR6* in PBMCs and lesions. Following appropriate management , CCL20 level within sera and blister fluid was considerably reduced, also count of Th1/17 cells and Tc1/17 cells [1].

levels of CCL20 in PBMCs were related to disorder severity of other autoimmune disorders like IBD, [22] that correlated with with the current results.

On the other hand, **Fujimura and his colleagues**; have demonstrated that there were no significant associations were identified among CCL20, and the development of vitiligo (P = 0.39) [23]. The discrepancies among results may be due to the fact that **Fujimori's** study analyzed CCL20 within anti-PD1 antibody management, the pathogenesis of vitiligo vary from those within earlier findings which analyzed a single time point within traditional vitiligo [23].

The actual mechanism of vitiligo-mediated CCL20 could be due to the fact that IL-17 is an effective stimulator of chemokine CCL20 formation, that drives movement of cytotoxic CD8+ T cells from systemic circulation to peripheral tissues [23, 24].

Our study revealed that there was a significant positive association among VETF score and CCL20 levels, while there wasn't any significant positive association among duration of disease and CCL 20 levels. This came in accordance with **AL-Mousawi and his colleagues;** who have showed that there wasn't any significant correlation between CCL20 level and disease duration among vitiligo-affected subjects (whether active or stable) [19].

CONCLUSION

The current study concluded that serum level of CCL20 was demonstrated to be correlated positively with vitiligo-affected patients. Additionally, it seems to have a positive association with disease activity however not with disorder duration. Thus it could be used as a reliable predictor for vitiligo development as well as its activity.

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