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Serum level of YKL-40, C-reactive protein and ESR in Patients with Vitiligo

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Abstract

Background: Vitiligo is a multifactorial disorder that associated with the destruction of melanocytes resulting from immune and inflammatory mediators. The most important theory about the pathogenesis of vitiligo is the autoimmune theory in which cytokines and inflammatory mediators such as GM-CSF, TNFα, IL6, IL1 and IL8 play a key role. YKL-40 is one of the major secreted proteins from human articular chondrocytes, synovial cells, endothelial cells and macrophages, and expressed by mature neutrophils.It is suggested that it participates in many physiological and pathological processes such as proliferation, angiogenesis, mitogenesis and remodelling. C-reactive protein is an acute phase protein secreted in the blood stream by the liver in response to inflammatory cytokines such as IL6 and several other systemic inflammation biomarkers. ESR is routinely measured in clinical practice, as an indicator of infection, sepsis, or autoimmunity and malignancy. The aim of this study was to evaluate serum level of YKL-40, hs-CRP and ESR in vitiligo patients in comparison with normal controls. Methods: This study included 40 vitiligo patients, and 40 apparently healthy volunteers who served as controls. The patients were recruited from the outpatient clinic of Dermatology and Andrology Department of Benha University Hospitals. Results: Regarding the course of vitiligo ,92.5% of the studied cases had active disease. The most common sites of vitiligo were upper limb, face and lower limb and 45% of the cases had lesions in two sites. The serum level of YKL-40, hs-CRP and ESR were significantly higher in vitiligo patients compared to control. Conclusion: This study showed that YKL-40, hs-CRP and ESR levels were elevated in vitiligo patients. Thus, there is a relation between vitiligo and inflammation. From the results of the present study, it is concluded that serum YKL-40 may play a role in vitiligo pathogenesis.

Key words: YKL-40– C-reactive protein, ESR, Vitiligo

1. Introduction

Vitiligo is an acquired, idiopathic disorder characterized by circumscribed depigmented macules and patches, which affect approximately 0.1–2% of the general population worldwide. Vitiligo may appear any time from shortly after birth to senescence. The average age of onset is variable, but peaks in the second and third decades. The exact pathogenesis of vitiligo is uncertain [1] . It is a multifactorial disorder related to both genetic and non-genetic factors [2]. The pathogenesis of vitiligo is associated with the destruction of melanocytes resulting from immune and inflammatory mediators. The most important theory about the pathogenesis of vitiligo is the autoimmune theory in which cytokines and inflammatory mediators such as GM-CSF, TNFα, IL6, IL1, and IL8 play a key role [3].

Hypersensitive C-reactive protein (hs-CRP) test is a quantitative laboratory test that analyzes very low amounts of CRP in the serum. CRP is an acute phase protein secreted in the blood stream by the liver in response to inflammatory cytokines such as IL6 and several other systemic inflammation biomarkers [4].

Standard CRP (normal levels of 0-0.5 mg/L) has been used for years in patients with acute inflammation or for evaluating evident chronic inflammation. A level of less than 1 mg/L is considered low risk, 1-3 mg/L as a medium risk, and more than 3 mg/L as a high-risk inflammation. For levels more than 10 mg/L the source of inflammation or infection should be sought and the test should be repeated after recovery [5].

Chitinase-3-like protein 1 (CHI3L1), also known as YKL-40, is a secreted glycoprotein that is approximately 40kDa in size. It is encoded in humans by the CHI3L1 gene [6]. YKL-40 is expressed and secreted by various cell types including macrophages, chondrocytes, fibroblast-like synovial cells, vascular smooth muscle cells, and hepatic stellate cells. The biological function of YKL-40 is unclear. It is not known to have a specific receptor. Its pattern of expression is associated with pathogenic processes related to inflammation, extracellular tissue remodeling, fibrosis and solid carcinomas and asthma [7].

Based on the above-mentioned information, the aim of this study was to measure serum level of YKL-40, hs-CRP and ESR in vitiligo patients and elucidate any possible association with disease severity.

2. Subjects and Methods

Subjects

This case-control study was conducted on forty vitiligo patients and forty age and sex matched healthy volunteers served as controls. They were recruited from the outpatient clinic of Dermatology, Andrology and Venereology Department of Benha University Hospitals during the period from October 2020 to March 2021.

Inclusion criteria

The study was conducted on patients above the age of 18 years diagnosed with vitiligo.

Exclusion criteria

Any patient presented with any of the following conditions will be excluded from the study

- Patients receiving systemic or topical anti-vitiligo therapy one month prior to the study.
- Pregnant or lactating.
- Any conditions that could affect YKL-40, CRP and ESR levels such as:
- Smoking or high blood pressure.
- Coexistent of chronic inflammatory disorders other than vitiligo such as rheumatic diseases, psoriasis, inflammatory bowel disease (IBD), etc. As well as those having specific underlying diseases such as coronary artery disease, atherosclerosis, metabolic disease, and chronic pulmonary disease.
- Patients giving the history of or presenting with signs and symptoms suggestive of acute viral, bacterial or parasitic infections 2 weeks prior to the study.
- History of using anti-inflammatory drugs, or corticosteroids.

Ethical consideration

- Before taking blood samples, a written informed consent was taken from each participant.

Administrative design

- This study was approved by the Research Ethical Committee of Benha Faculty of Medicine, and was carried out according to the guidelines of the Helsinki declaration principles.

Methods

All patients were subjected to:

- **Full history taking including** demographic data (sex and age), medical history (atherosclerosis, cancer,etc.), and family history.
- **Clinical examination** to assess onset of the disease, disease duration and severity.

Assessing the severity of vitiligo

To evaluate the severity of vitiligo, Vitiligo Extent Tensity Index (VETI) score was used [8]. The VETI score is a new system that proposes to measure the extent of vitiligo by a numerical score and combines analysis of extensity and severity of vitiligo and produce a constant and reproducible number like Psoriasis Area and Severity Index (PASI). The percentage of extension involvement (p) evaluates using the rule of nines already used in burn assessment. Five sites affected, head (h), upper limbs (u), trunk (t) and lower limbs (l) and genitalia (g) are separately scored by using five stages of disease tensity (T):

- Stage 0: normal skin.
- Stage 1: hypopigmentation (including trichrome and homogeneous lighter pigmentation).
- Stage 2: complete depigmentation with black hair and with perifollicular pigmentation.
- Stage 3: complete depigmentation with black hair and without perifollicular pigmentation.
- Stage 4: complete depigmentation with compound of white and black hair with/without perifollicular pigmentation.
- Stage 5: complete depigmentation plus significant hair whitening.

The total body VETI is calculated using the following formula that includes contributions from all body regions: VETI score: (percentage of head involvement × grade of tensity) + (percentage of trunk involvement × grade of tensity) 4+ (percentage of upper limbs involvement × grade of tensity) 2+ (percentage of lower limbs involvement × grade of tensity) 4+ (percentage of genitalia involvement × grade of tensity) 0.1

The coefficients reported in this formula are based on percent of skin surface by the rule of nines. Accordingly, the coefficient of head is 1 (9:9=1), trunk and lower limb is 4 (36:9=4), upper limb is 2 (18:9=2) and genitalia is almost 0.1(1:9= 0.1).

VETI: (Ph×Th) +(Pt×Tt)4+(Pu×Tu)2+(Pl×Tl)4+ (Pg×Tg)0.1

5+20+10+20+0.5=55.5

The maximum score of VETI is 55.5.

Percentage of involvement: P Tensity: T

There are other methods can be used for assessing the severity of vitiligo in addition to VETI score as Vitiligo Area Scoring Index (VASI) score [9], which is conceptually derived from the PASI score widely used in psoriasis assessment. The total body VASI is calculated using a formula that includes contributions from all body regions (possible range, 0–100).

VASI= ∑ All Body Sites [Hand Units] × [Residual Depigmentation]

One hand unit, which encompasses the palm plus the volar surface of all the digits, is approximately 1% of the total body surface area and is used as a guide to estimate the baseline percentage of vitiligo involvement in each body region. The body is divided into five separate and mutually exclusive regions: hands, upper extremities (excluding hands), trunk, lower extremities (excluding feet), and feet. The axillary region is included with the upper extremities while the buttocks and inguinal areas are included with the lower extremities. The extent of residual depigmentation is expressed by the following percentages: 0, 10%, 25%, 50%, 75%, 90%, or 100%. At 100% depigmentation, no pigment is present; at 90%, specks of pigment are present; at 75%, the depigmented area exceeds the pigmented area; at 50%, the depigmented and pigmented areas are equal; at 25%, the pigmented area exceeds the depigmented area; at 10%, only specks of depigmentation are present.

Laboratory investigation

Venous blood samples (5ml) were taken from all studied subjects and divided into two tubes one citrated blood for ESR and one plain tube for serum separation to evaluate level of hs-CRP & YKL-40 by using enzyme-linked immunosorbent assay (ELISA)

technique. Serum separating tube was left at room temperature for 30 minutes till coagulation, and then was centrifuged. The resultant serum stored at −20°C until analysis.

Measurement of serum level of YKL-40:

A double-antibody sandwich ELISA (Enzyme Linked Immune Sorbent Assay) was used to detect serum level of YKL-40 using a commercial Human YKL-40 ELISA Kit.

Measurement of serum level of hs- CRP:

Serum levels of hs-CRP were done by ELISA kits.

Measurement of ESR

Westergren method

The Westergren method requires collecting 2 ml of venous blood into a tube containing 0 .5 ml of sodium citrate. It should be stored no longer than 2 hours at room temperature or 6 hours at 4 °C. The blood is drawn into a Westergren-Katz tube to the 200 mm mark. The tube is placed in a rack in a strictly vertical position for 1 hour at room temperature, at which time the distance from the lowest point of the surface meniscus to the upper limit of the red cell sediment is measured. The distance of fall of erythrocytes, expressed as millimeters in 1 hour, is the ESR[10].

Statistical analysis

The collected data was revised, coded and tabulated 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.

3. Results

Table (1) Demographic data of the studied groups

Variable		Cases (n=40)		Control (n=40)		Test	P
Age: (years)	Mean ± SD	28.03 ± 10.15		29.83 ± 8.16		MW	
	Range	18 – 55		19 – 50		1.54	0.12
	Median (IQR)	23 (20-34)		28(24-35)			NS
BMI: (Kg/m^2)	Mean ± SD	24.12 ± 3.8		25.1 ± 4.01		t	
	Range	17.3 – 32.7		17.9 – 32.7		1.13	0.26 NS
	Variable	No	%	No	%	χ^2	P
Gender:	Male	12	30	14	35	0.23	0.63
	Female	28	70	26	65		NS

SD: Standard deviation IQR: Inter quartile range MW: Mann Whitney test t: Independent t test
χ^2: Chi square test NS: Non significant (P>0.05)

This table shows that there were no statistical significance differences between the studied groups regarding age, BMI and gender (P>0.05).

Table (2) History of the cases' group.

Variable		Cases (n=40)	
Duration: (years)	Mean ± SD	5.9 ± 6.35	
	Range	1 – 30	
	Median (IQR)	4 (2.25-6.75)	
Variable		**No**	**%**
Family history:	-ve	15	37.5
	+ve	25	62.5
History of associated diseases:	No	40	100
	Yes	0	0
History of previous ttt:	No	40	100
	Yes	0	0

SD: Standard deviation IQR: Inter quartile range

This table shows that the disease duration among the cases' group ranged from 1 to 30 years with median 4 years. Also 62.5% of the cases had positive family history. None of the cases had history of neither associated diseases nor previous treatment.

Table (3) Clinical data of the cases' group.

Variable		Cases (n=40)	
		No	%
Course:	Active	37	92.5
	Stable	3	7.5
Site:	Face	16	40
	Pre-orbital	3	7.5
	Breast	2	5
	Trunk	9	22.5
	UL	17	42.5
	Hand	6	15
	LL	13	32.5
	Foot	5	12.5
	1 site	15	37.5
	2 sites	18	45
	3 sites	6	15
	4 sites	1	2.5
VASI score:	Mean ± SD	3.83 ± 3.44	
	Range	0.5 – 14.25	
	Median (IQR)	2 (1.4 – 5.34)	
VETI score:	Mean ± SD	5.72 ± 4.41	
	Range	0.5 – 20.5	
	Median (IQR)	4.75(2.5-7.33)	

SD: Standard deviation IQR: Inter quartile range

This table shows that 92.5% of the studied cases had active disease. The most common sites of vitiligo were upper limb (42.5%), face (40%) and lower limb (32.5%) and 45% of the cases had lesions in two sites. VASI score ranged from 0.5 to 14.25 with median 2 and VETI score ranged from 0.5 to 20.5 with median 4.75.

Table (4) Comparison of the studied markers among the studied groups

Variables		Cases (n=40)	Control (n=40)	MW	P
YKL-40: (ng/ml)	Mean ± SD	121.29 ± 85.09	14.88 ± 5.46		
	Range	17.4 - 290.7	7.1 – 30	**7.44**	**<0.001**
	Median (IQR)	129.6 (36.98-188.68)	13.6 (11.83-16.25)		****
hs-CRP: (mg/l)	Mean ± SD	23.74 ± 9.51	1.99 ± 1.37		
	Range	4.2 – 38.7	0.33 – 4.8	**7.68**	**<0.001**
	Median (IQR)	23.95(16.5-31.05)	1.69(0.76-3.1)		****
ESR: (mm/hr)	Mean ± SD	46.65±21.56	9.45 ± 2.69		
	Range	8 – 103	5 – 15	**7.11**	**<0.001**
	Median (IQR)	43 (34.5-56.5)	9 (7 – 11)		****

SD: Standard deviation IQR: Inter quartile range MW: Mann Whitney test **: Highly significant (P<0.001)

This table shows, that vitiligo patients had statistically significant higher values of YKL-40, hs-CRP and ESR compared to control group (P<0.001)**.**

4. Discussion

In our study out of 40 patients, 30% were males while 70% were females indicating preponderance of vitiligo in female. This came in agreement with Sarkar et al. [11] and Akay et al. [12] study which showed female preponderance in vitiligo. This is because women notice the change in appearance and approach doctors sooner than men, due to cosmetic reasons. While, Kyriakis et al. [13]found that vitiligo equally affects men and women. This difference may be due to different sample size.

In our study we found that the mean age of patients was 28.03±10.15 years and the disease duration ranged from 1 to 30 years with median 4 years. This came in agreement with Abdel-Megaid et al. [14] who found that vitiligo often begins in young adulthood. Almost half of the affected individual initially afflicted before the age of 25 and its prevalence decreases with age.

In the current study we found that 25 cases out of 40 (62.5%) had positive family history and none of the cases had history of neither associated diseases nor previous treatment. This result was similar to

Sarkar et al. [11] who found that 29 cases out of 70 (41.4%) had positive family history. They also revealed that 10.0% of patients had children with vitiligo indicating a higher familial incidence.

Our study shows that 92.5% of the studied cases had active disease. The most common sites of vitiligo were upper limb (42.5%), face (40%) and lower limb (32.5%) and 45% of the cases had lesions in two sites.

This came in agreement with Alikhan et al. [15] and Kalkanli and Kalkanli [16], they found that the most common manifestation of vitiligo is the generalized type in the form of bilateral symmetrical depigmentation and the most common sites were the face, neck, extensor surfaces or bony surfaces on the hands, feet, wrists, axilla and mucosal surfaces.

The present study revealed that the mean serum hs-CRP level and ESR were significantly higher in vitiligo patients compared to control. This result came in agreement with Sarkar et al. [11], they found that the mean serum hs- CRP in case group was significantly higher than control group. Moreover, Ghaderi and Nezafati [17], found higher levels of hs-CRP in patients with generalized vitiligo compared to other types as well as to control group.

Joo et al. [18] found that ESR and C-reactive protein level were elevated in vitiligo patients.

As several mechanisms of melanocytes destruction in vitiligo have been proposed, autoimmune and inflammatory cytokine hypothesis are the most widely accepted theories which play a key role in vitiligo pathogenesis. TH-17 cell was found to be increased in the serum and epidermis of vitiligo patients with active lesions and also raised levels of pro-inflammatory cytokines GM-CSF, TNF-α, IL-1β, IFN-γ and IL-10 by innate cell like natural killer (NK) cells as well as ESR and CRP [19].

In this study we found that hs-CRP and ESR were significantly positively correlated with VASI score and VETI score among the cases'group. Also, they had significant positive correlation with the duration of disease. This came in agreement with Sarkar et al. [11], they found that hs-CRP was significantly positively correlated with VASI score in vitiligo patients. They even suggested that serum hs-CRP level might be a useful index for evaluating the disease activity of vitiligo as a novel biomarker. Moreove, the study of Sarkar et al. [11] declared that hs-CRP had positive statistically significant correlation with duration of disease.

In the present study there was no significant relation between hs- CRP neither to sex nor to BMI. This came in agreement with Ghaderi and Nezafati [17], who found that the serum level of hsCRP did not differ between the studied groups with respect to sex and BMI.

To the best of our knowledge, this is the first study to measure YKL-40 level in vitiligo patients.

Our results revealed that serum level of YKL 40 was significantly higher among vitiligo patients when compared to control group. This result supports the previous findings suggesting that YKL-40 is a possible reliable biomarker in different acute and chronic inflammatory and autoimmune disorders. Although its biological function is not completely understood, it seems to be a marker of inflammation and tissue remodeling [20].

With in-depth investigations, it has been reported that YKL-40 could promote the secretion of pro-inflammatory cytokines, such as IL-6 and TNF-α, through activating the nuclear factor-κB (NF-κB) signalling pathway, which resultantly facilitates the pathogenesis of inflammation [21].

Moreover, several studies [22, 23, 24] reported high levels of cytokines and inflammatory mediators such as GM-CSF, TNFα, IL6, IL1, and IL8 in vitiligo patients.

The relation between vitiligo and inflammatory mediators was also asserted by Lv et al. [25]; they reported complete fading of vitiligo lesions after being treated by infliximab (an anti-TNF-α agent). Therefore,they hypothesized that TNF-α plays an important role in vitiligo.Therefore, we could reasonably speculate that serum YKL-40 levels may be useful as a biomarker for vitiligo diagnosis.

Elevation of YKL-40 was also observed in other inflammatory and autoimmune diseases such as Rheumatoid arthritis [20], Behcet's disease [26], familial Mediterranean Fever [27], Crohn's disease [28], Psoriasis [29], Atopic dermatitis [30], and alopecia areata [31].

Aside from the inflammatory theory, another aspect for the association between YKL-40 and vitiligo disease could be postulated. YKL-40 has also been confirmed to be highly expressed in atherosclerotic plaques and to be associated with the pathogenesis of cardiovascular diseases [32]. It was also demonstrated that the serum levels of YKL-40 were significantly elevated in patients with metabolic syndrome [33]. Like psoriasis, vitiligo is not merely a skin disease, and it is becoming increasingly recognized as a systemic condition in which patients may be at a higher risk of developing metabolic syndrome, atherosclerosis, and cardiovascular diseases [34]. Taken together, this could open new perspectives in the association between vitiligo and YKL-40 and emphasize the importance of YKL-40 as a marker for disease activity.

5. Conclusion

This study showed that YKL-40, hs-CRP and ESR levels were elevated in vitiligo patients. Thus, there is a relation between vitiligo and inflammation.

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