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Assessment of Serum Level of Chitinase-3-Like Protein-1 (Ykl-40) in Systemic Lupus Erythematosus Patients and Its Relation to Disease Activity

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Systemic Lupus Erythematosus (SLE) is a multisystem autoimmune disorder where such progress and prognosis cannot be anticipated. Chitinase-3-like protein 1 (YKL-40) is a multifunctional pro-inflammatory protein that plays a crucial role in immunity and inflammation, as well as in the control of cell differentiation, proliferation, and apoptosis.

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Aim of the Work: To investigate the serum level of YKL-40 in SLE patients contrasted to healthy controls and to link it with symptom severity and organ involvement.
Patients and Methods: A total of 50 subjects; 25 SLE patients and 25 healthy controls matched for age and sex were enrolled in this cross-sectional study. The circulating level of YKL-40 was determined using the ELISA technique in patients and controls and was shown to correlate with clinical and laboratory results in SLE patients.
Results: Serum YKL-40 levels were considerably greater in SLE patients compared to controls (P≤ 0.001) and positively correlated with disease activity., ESR, CRP and serum creatinine level. Serum YKL-40 was greater in SLE patients with malar rash, fever and arthralgia and has no relation to lupus nephritis.
Conclusion: During active disease phases, serum YKL-40 may have a role in the inflammatory aetiology of SLE. It may serve as a valuable laboratory test in the future for detecting SLE activity and joint inflammation.

Keywords: Chitinase-3-like protein-1 (YKL-40); Systemic lupus erythematosus, joint inflammation.

1. INTRODUCTION

Systemic lupus erythematosus (SLE) defined as a chronic autoimmune inflammatory illness that primarily impacts the lungs, heart, kidneys, joints, skin, liver, blood vessels and neurological system [1].

Although SLE aetiology is still unidentified, many regulatory and pathogenic B cell subtypes have been implicated in SLE pathogenesis [2].

Macrophages are multifunctional phagocytic cells with regulatory roles in the immune system. However, macrophage clearance of apoptotic cells is impaired in SLE. In addition, neutrophils have appeared as key participants in SLE pathogenesis, and they are linked with an elevated risk of developing atherosclerosis and vascular damage [3].

YKL-40 is a glycoprotein related with inflammation having a molecular weight of 40 kDa. YKL-40 is an acronym derived from the one-letter codes for the first three N-terminal amino acids, tyrosine (Y), lysine (K), and leucine (L) [4].

It is a member of the chitinase-like protein family lacking the enzymatic activity of actual chitinases. Chondrex, chitinase-3-like protein 1 (Chi3-L1), human cartilage glycoprotein 39 and breast regression protein 39 (BRP-39) are alternative names for YKL-40. Increased concentrations of YKL-40 have been connected to inflammation, tissue remodeling, and cancer [5].

YKL-40 is regulated in many cell types and its levels have been linked to inflammation, tissue remodeling, and cancer. Multiple inflammatory cells, including fibroblasts, macrophages, chondrocytes, neutrophils, endothelial cells, and smooth muscle cells, produce and release this protein. YKL40 is integrated into both innate and adaptive type 2 immune processes, according to certain research, and its significance in inflammation, angiogenesis, tissue remodeling, and cell proliferation is suggested [6-10]. This protein's function in atopic dermatitis, psoriasis, Behcet's illness, and lichen planus has been examined [11-13].

YKL-40, as an inflammatory mediator may play a role in SLE and its inflammatory tissue destructive cascades.

2. METERIALS AND METHODS

2.1 Study Design

This cross sectional included 25 adult patients with SLE diagnosed according either 1997 ACR revised criteria [14] or 2012 SLICC criteria [15] for SLE classification in addition to 25 healthy subjects of matched age and sex who as controls. They were admitted from the Outpatient Clinics of Dermatology and Venereology Department and Rheumatology Unit of Internal Medicine Department, Tanta University Hospitals in the period from September 2020 to December 2021.

2.2 Methods

Every patient was exposed to the following: Complete history taking including: Age, sex, occupation, history of habitual sun exposure, age of onset of the disease, family history, drug history, history of other autoimmune diseases. Thorough clinical examination with special attention to cutaneous manifestations. Quirky skin lesions were furtherly assessed by

dermoscopy, and skin biopsy was taken for histopathology when needed. Laboratory investigations were done for SLE cases in the form of: Complete blood count (CBC), serum creatinine and blood urea nitrogen, complete urine analysis, 24-h urine proteinuria, ESR, CRP, Antinuclear antibodies (ANA) titer, Anti-ds-DNA titer, C3 and C4, Antiphospholipid antibodies, renal biopsy when directed based on the ACR guidelines for management and screening of lupus nephritis. Serum level of YKL-40 was estimated by ELISA technique [Human chitinase protein 40 (YKL-40) ELISA kit, Shanghai Hengyuan Biology, HB 1384-Hu, China] for both patients and controls and evaluation the SLE disease activity index (SLEDAI) [16] was don for SLE patients , no activity (SLEDAI=0), mild activity (SLEDAI=4 to 7), moderate activity (SLEDAI=8 to 12) and sever activity (SLEDAI= >12). According to the SLEDAI score, the participants were aliquoted into three groups: cases with mild activity (n = 7); cases with moderate activity (n = 9); cases with severe activity (n = 9).

2.3 Statistical Analysis

Data were inputted into the computer and analyzed using version 20 of the IBM SPSS software program (Armonk, NY: IBM Corp). According to the type of data acquired for each parameter, the appropriate analysis was performed, and results were displayed with significant value <0.05.

3. RESULTS

Demographic data are shown in Table 1 where there was insignificant difference was detected between SLE patients' group and controls regarding age, gender or history of sun exposure.

Systemic manifestations are shown in Table 2 where the common manifestations were malar rash, arthralgia and oral ulcers while discoid lesions and peripheral were the least common manifestations.

Laboratory investigations in SLE cases and controls are displayed in Table 3.

Specific lupus tests in SLE patients are shown in Table 4.

Regarding the serum level of YKL–40: in the control group, it ranged from 3.6 –52.9 µg/L with a mean of 11.4 µg/L ± 9.6 (SD). In SLE patients' group, it ranged from 2.5 – 873 µg/L with a mean of 235.4 µg/L ± 293.3(SD). Serum level of YKL–40 was remarkably higher in SLE cases contrasted to controls (P value < 0.001) (Table 5).

Table 6 compares YKL-40 between lupus patient with different disease activity, there was considerable variation in YKL–40 level between different grades with the highest level in cases with severe SLE with median 685.5, moderate level in cases with moderate SLE with median 139.6 and lowest level in cases with mild SLE with median 15.70 (Table 6).

Table 1. Demographic data

	Cases (n = 25)		Control (n = 25)		Test of Sig.	P
	No.	%	No.	%		
Sex						
Male	3	12	8	32	χ^2=	0.088
Female	22	88	17	68	2.914	
Age (years)						
Min. – Max.	19– 45		20– 45		t=	0.075
Mean ± SD.	32.84 ± 8.28		26.72 ± 6.65		1.825	
Median (IQR)	35 (26– 39)		25 (22– 3)			
Habitual sun exposure						
Prolonged exposure	16	64	11	44	χ^2=	0.156
Mild exposure	9	36	14	56	2.013	
Disease duration (years)						
Min. – Max.	2-13		–		–	–
Mean ± SD.	4.77 ± 4.43		–			
Median (IQR)	5 (0.5 – 8)		–			

IQR: Inter quartile range; SD: Standard deviation; χ^2: Chi square test; t: Student's t-test
P: P-value used to compare the two investigated groups
**: Statistically significant at P ≤ 0.05*

Table 2. Systemic manifestations

Systemic manifestations	Percentage
Malar rash	60%
Arthralgia	60%
Oral ulcers	32%
Photosensitivity	30%
Malaise	25%
Serositis	22%
Fever	20%
Alopecia	15%
Discoid lesions	12%
Photosensitivity	10%

Correlation between YKL–40 and laboratory findings in SLE patients' group are shown in Fig. 1; there was significant positive correlation between serum YKL-40 level and serum creatinine level, CRP, ESR and SLEDAI score but there was insignificant correlation between serum YKL-40 level and either patients' age, disease duration, Hb level, WBCs count, platelet count, blood urea nitrogen level, urinary 24-hour protein C4, C3, Anti ds DNA or ANA.

4. DISCUSSION

SLE is a chronic autoimmune disorder that may affect any organ system, including the heart, kidneys, skin, lungs, neurological system, joints, and serous membranes. Its appearance and direction are quite diverse, ranging from tranquil to sudden [17].

There is always need for new marker to diagnose disease and assess activity. The aim is to have a perfect marker easy, cheap and available and to research for relation with disease activity and lupus nephritis.

Various risk factors have been found and proved making a meaningful contribution to disease pathogenesis or activating the immune system, resulting in an inflammatory response that eventually leads to the illness development [18,19].

YKL-40 is a member of the glycosyl hydrolase 18 protein family, which is distinguished by its ability to break the polysaccharide chitin. Numerous cytokines and hormones, including IFN-, IL-6, IL-17, IL-13, vasopressin and parathyroid hormone-related proteins are known to affect the expression of YKL-40 in different cell types [20].

The YKL-40 chitinase has been the subject of the greatest research into numerous human disorders. Serum levels of YKL-40 have been shown to be elevated in several inflammatory disorders, including Crohn's disease, RA, and various cardiovascular conditions [20,22]. Unfortunately, its role in SLE hasn't been well investigated yet and literature about it in this disease is very sparce.

Table 3. Laboratory investigations in SLE cases

CBC	Cases (n = 25)	Control (n = 25)	Test of Sig.	P
Hb g/dl				
Min. – Max.	6– 12.40	12– 15	t= 10.444*	<0.001*
Mean ± SD.	9.99 ± 1.44	13.54 ± 0.90		
PLT x10^3/mm^3				
Min. – Max.	90– 359	190– 300	t= 0.592	0.558
Mean ± SD.	241.3 – 76.90	251.4 ± 35.81		
WBCs x10^3/mm^3				
Min. – Max.	1.90 – 22	4.50 – 9.20	U= 272.0	0.431
Median (IQR)	7 (5– 8.20)	7.50 (6– 8.70)		
Urea mg/dl				
Min. – Max.	18– 65	20– 33	t= 2.293*	0.030*
Mean ± SD.	32.68 ± 12.81	26.56 ± 3.74		
Creatinine mg/dl				
Min. – Max.	0.40 – 3.30	0.20 – 1	U= 111.5*	<0.001*
Mean ± SD.	0.80 (0.60 – 1.40)	0.50 (0.40 – 0.70)		
Protein mg /24 h				
Min. – Max.	22– 724	12.50 – 70	U= 44.500*	<0.001*
Median (IQR)	113 (66– 222)	30 (22– 40)		

*IQR: Inter quartile range; SD: Standard deviation; t: Student t-test; U: Mann Whitney test; p: P-value used to compare the two investigated groups; *: Statistically significant at p ≤ 0.05*

Table 4. Specific lupus tests in SLE patients

	SLE patients (n = 25)
Anti–dsDNA (IU/ml)	15 (60%)
Min. – Max.	2.15 – 99
Median (IQR)	31 (12.30 – 55)
ANA (IU/ml)	19 (76%)
Min. – Max	0.3 – 500
Median (IQR)	20 (2.10 – 77)
Lupus anticoagulant (LAC)	3 (12%)
Anti-cardiolipin antibodies	1 (4%)
Renal biopsy	
Not done	21 (84%)
Class III nephritis	3 (12%)
Class IV nephritis	1 (4%)
CRP (mg/L)	
Min. – Max	1– 24
Median (IQR)	10 (4.50 – 15)
ESR 1st hour (mm/hr)	
Min. – Max	6 – 90
Median (IQR)	30 (20 – 50)
ESR 2nd hour	
Min. – Max.	15– 119
Median (IQR)	65 (47 – 80)
C3 (mg/dl)	
Min. – Max.	6– 159
Median (IQR)	54 (43 – 97)
C4 (mg/dl)	
Min. – Max.	5– 75
Median (IQR)	10 (9 – 17)

C3: complement 3; C4: complement 4; CRP; C-reactive protein; IQR: Inter quartile range; SD: Standard deviation

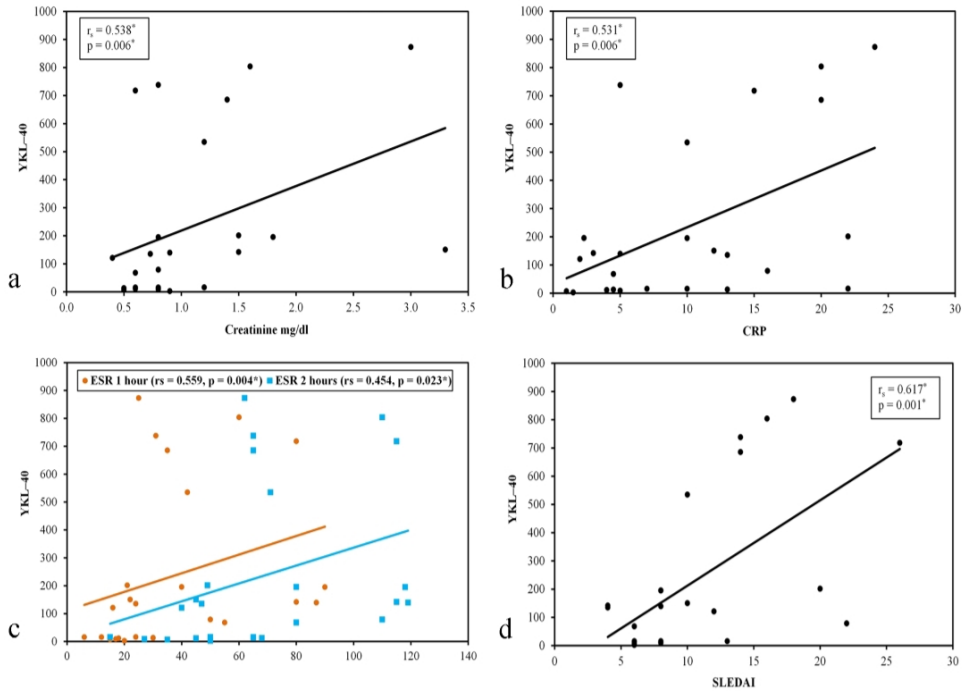

Fig. 1. Correlation between YKL–40 and laboratory findings in SLE patients' group

Table 5. Serum level of YKL–40

YKL–40 (µg/L)	SLE patients (n = 25)	Control (n = 25)	U	P
Min. – Max.	2.5 – 873	3.6 – 52.9	88.50*	<0.001*
Median (IQR)	135.3(15.7 – 201.4)	9 (6.9 – 11.8)		

*U: Mann Whitney test; IQR: Inter quartile range; P: level of significance for comparing two studied groups; *: Statistically significant at P ≤ 0.05*

Table 6. SLEDAI score

YKL–40 µg/L	SLEDAI score			H	P
	Mild (n = 7)	Moderate (n = 9)	Severe (n = 9)		
Min. – Max.	2.5 – 141.9	8.9 – 534.8	15.9 – 873	8.763*	0.013*
Median (IQR)	15.70 (10.25–101.8)	139.6 (12.60 –95.2)	685.5 (121.3 – 738.0)		
Pairwise	p_1=0.302, p_2=0.004*, p_3=0.049*				

*H: H for Kruskal Wallis test, pairwise comparison bet. Post Hoc Test (Dunn's test for multiple comparisons) was used to compare each 2 groups; P: level of significance to compare SLEDAI of SLE patient and YKL–40; P_1: level of significance to compare Mild and Moderate; P_2: level of significance to compare Mild Severe; P_3: level of significance to compare Moderate and Severe; *: Statistically significant at P ≤ 0.05*

In the current cross-sectional investigation, the ratio of females to males among SLE patients (n=25) was 7.3:1and this female predominance in SLE has been repeatedly described in previous literatures [23,24,25].

Also, the SLE patients mean age was 32.8 years ± 8.3 (SD). SLE is often described as a disease that most often strikes reproductive-age women with some differences among ethnic groups [26].

Patients with SLE had considerably greater serum YKL-40 levels than healthy controls (P <0.001). This may be due to the increased synthesis of YKL-40 in inflammatory conditions, when a variety of cells, including neutrophils, macrophages, endothelial cells, chondrocytes, and fibroblasts, smooth muscle cells, participate to its production. YKL40 is a component of both innate and adaptive type 2 immune systems, and it plays a significant role in autoimmunity and inflammation [25].

Also, the current study detected a significant positive correlation between serum YKL-40 and activity of SLE as evaluated by SLEDAI scores [17]. So elevated YKL-40 level might be a future helpful tool to observe disease progression and to manage therapy in SLE patients [17].

The production and secretion of YKL-40 are controlled by stress, growth factors, cytokines, changes in the extracellular matrix, and medications. Several studies suggest that YKL-40 may serve as a marker of tissue remodeling, inflammation, fibrosis, proliferation, and angiogenesis in a variety of ailments, such as cancer, inflammation, infections, dermatoses, and cardiovascular diseases [27].

Once released, YKL-40 has a manifest role in the regulatory production of inflammatory cytokines which relate to the severity of inflammatory disease conditions and aggressiveness of autoimmunity, and this could be contributed to its considerably greater levels in SLE patients with more disease activity. The discrepancy inflammatory cytokines production like IL-1, TNF-*α*, interferons type I and II, IL-6and IL-10 related to immune disruption and promote inflammation in SLE tissues and organ impairment [29,30]. Multiple studies have linked B- and T-cell hyperactivity as well as autoantibody formation to high levels of these pro-inflammatory cytokines [29-32]. Some early research found contradictory correlations between SLE patient blood concentrations of inflammatory cytokines and disease activity [33,34].

In our study, serum YKL-40 had a significant positive correlation with ESR and CRP which are among the traditional indicators of disease activity in SLE. ESR and CRP are positive acute phase reactants which are inflammation markers that are significantly elevated, and their concentrations increase during inflammation (they include procalcitonin, CRP, ferritin, hepcidin, fibrinogen and serum amyloid A.) [35].

By tracking how quickly the erythrocytes settle within a vertical tube for one hour, ESR may be used as a proxy for fibrinogen concentration.

Within the first 48 hours of inflammation, the ESR begins to climb. The elevation of ESR is a potential marker of inflammation [36].

CRP levels have been linked to constitutional, neuromotor, ocular, gastrointestinal, pulmonary, and laboratory domains of disease activity in cohorts of SLE patients, according to some research. There is evidence linking CRP to SLE-related tissue damage as well [37].

Acute phase reactants have important role as mediators produced during acute and chronic inflammatory states. Interleukin-6, IL-1, TNF-α, and IFN-γ can also stimulate the acute-phase reactants production. These inflammatory cytokines play a critical role in SLE pathogenesis [38]. in the present study, YKL-40 was considerably correlated with elevated ESR and CRP. Therefore, it might be a promising future tool that helps in detecting inflammatory disease activity in SLE in a condition similar to the known acute phase reactants.

Despite a statistically significant positive association between serum YKL-40 level and serum creatinine level, no statistically significant relationship was found between serum YKL-40 level and either the existence or severity of lupus nephritis. This may be a result of the study's limited sample size and number of individuals with lupus nephritis. YKL-40 has been reported as a developing biomarker in kidney illness, an indication of the degree of renal tubular damage, and a factor in preventing tubular cell death during the healing phase of acute kidney ischemia [39].

To date, YKL-40 has been examined extensively in urine samples as a biomarker for kidney disease, but not in blood samples [40]. Elevated urine YKL-40 levels have been connected with the requirement for dialysis in kidney transplantation [39], and in experimental and clinical settings, urine YKL-40 has been found to be a biomarker of structural kidney damage and inflammation [41,42]. Actually, there is an unmet need for larger scale studying of the serum and urinary changes of YKL-40 in patients with SLE and particularly in those at higher risk or who already have lupus nephritis of different grades, for better understanding of its role in renal insult. It might serve as a valuable biomarker that can identify cases with risk of progressive renal affection or those who may benefit from more intensified or targeted treatments against YKL-40.

Regarding the clinical symptoms of SLE in our investigation, serum YKL-40 was positively correlated with fever, malar rash, and arthralgia by a statistically significant value. Malar rash was the most prevalent dermatologic symptom (seen in 60% of patients). This might be due to the observation that individuals with malar rash had greater overall SLE disease activity at the time of diagnosis and continued to have higher disease activity at the one- and five-year follow-up points. Alternately, it may imply that individuals with malar rash acquire more severe disease symptoms later in their illness course, resulting in an increase in immunosuppressive usage after five years [43].

It is anticipated that the blood level of YKL-40 would be elevated in patients with lupus arthritis [44]. It is observed that numerous cell types in arthritic joints release YKL-40. It is a key protein released by arthritic knee joint chondrocytes [27]. Moreover, serum and synovial fluids YKL-40 levels were reported to be greater in joint illnesses such as osteoarthritis [45] and AR [46] and showing that YKL-40 is a marker of inflammation and tissue remodeling or degradation; YKL-40 is not detected in healthy joints [47].

Higher blood YKL-40 levels in RA patients compared to healthy controls were found, and these levels linked positively with disease activity, according to Jafari et al. results. YKL-40 is hypothesized to have a role as an autoantigen in RA. Possible pathogenic involvement for YKL-40 was reported in inflammation and destructive joint disease. As a result, YKL-40 was speculated to be a potential biomarker for estimating RA disease activity [47].

In our study, there was significantly positive relation between YKL-40 and lupus anticoagulant, but the small sample size makes this result still in need for future confirmation. It should be noted that increased thromboembolic complications were increased accompanying autoimmune diseases such as SLE. These could be due to the interconnection between thrombosis and inflammation processes and the association between high CRP level and interleukins (especially IL-6) with thromboembolic process [48,49]. YKL-40 as an inflammatory biomarker which increases in the serum during SLE activity is expected to be correlated with lupus anticoagulant presence and its elevated titers.

5. CONCLUSIONS

From this study it could be concluded that YKL-40 was significantly increased in SLE patients contrasted to controls and its serum level revealed a significant positive correlation with severity of lupus activity represented by SLEDAI score. Serum YKL-40 level correlated remarkably with acute phase reactants in the form of ESR and CRP and with serum creatinine.

6. LIMITATIONS AND RECOMMENDATIONS

In our study there was small number of patients with lupus nephritis so further multi centric studies on larger sample size are desired to emphasize our findings, to assess the underlying mechanisms for the increased level of YKL-40 in SLE and to evaluate the consequence of silencing YKL-40 on clinical status of SLE patient. Further studies with larger sample size are required to explain the relationship between urinary and serum YKL-40 level and lupus nephritis.

CONSENT AND ETHICAL APPROVAL

All patients provided informed consent in compliance with the local ethics committee. This research follows the ethical norms of the Helsinki Declaration and the ethical standards of the Tanta faculty of medicine. The confidentiality of all patient information was ensured by assigning a code number to each patient file including all investigations.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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