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Can Micro RNA-24 Affect the Cardiovascular Morbidity in Systemic Lupus Erythematosus by Targeting YKL-40?

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Abstract

Background: Systemic lupus erythematosus (SLE) is an autoimmune disease with inflammatory nature. One of the leading causes of death in SLE patients is cardiovascular (CVS) morbidity. MiRNA-24 is highly expressed in vascular endothelial cells (VECs). This dysregulated expression pattern is associated with dysfunction or even damage of VECs and leads to the occurrence of cardiovascular diseases. YKL- 40 is an inflammatory glycoprotein involved in the pathogenesis of endothelial dysfunction and thereby atherosclerosis. In this work, we aimed at illustrating the possible role of miR-24 and its target YKL-40 in the pathogenesis of the CVS morbidity associated with SLE.
Methods: This work was conducted on 40 SLE patients and 40 healthy controls. Quantitative real-time PCR (qPCR) was done to estimate the expression level of miRNA-24 in serum. In addition, we measured the serum level of YKL-40 using ELISA.
Results: miR-24-fold change was found to be down-regulated, whereas serum YKL- 40 was up-regulated among SLE patients with observed significant and negative correlation between the two parameters.
Conclusions: Our study provided an insight about the role of miR-24 and its target serum YKL-40 protein in the development of SLE-related inflammation and atherosclerosis.

Keywords: miRNA-24, SDC-1, SLE, VCAM, YKL-40.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease with inflammatory nature. It is characterized by increased activity of B-cells with overproduction of autoantibodies which attack different organs without specificity eventually contributing to the formation of immune-complexes; the deposition of which in the tissues and blood vessels results in inflammatory organ impairment (1).

One of the leading causes of death in SLE patients is cardiovascular (CVS) morbidity.

Multiple factors play a role in the pathogenesis of this morbidity including atherosclerosis and its precipitating factors, the inflammatory nature of SLE, autoantibodies, the acceleration of endothelial dysfunction, and finally SLE therapy (2). It was found from previous studies that autoantibodies cause oxidation of LDL particles, thus accentuating their atherogenic effect. In addition, they may exert a negative effect on the physiologically protective HDL particles. Endothelial dysfunction within the

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vascular system ensues, resulting in the development of atherosclerosis (3).

MicroRNAs (miRNAs) are gene expression and protein synthesis modulators that have been discovered in several species including humans. These miRNAs are single-stranded RNA molecules of about 20–25 nucleotides that are highly conserved among species. They are processed from primary transcripts (called pri-miRNA) to short stem-loop pre-miRNA and lastly to the functional miRNA (4).

miRNAs have been identified as regulators of immune cells development , and as a pivotal role players in the inflammatory response (5). In addition, numerous studies have provided significant results about the influence of Circulating miRNAs on either endothelium activation or damage (6). MiRNA-24 is one of the miR-23~27~24 family. It is highly expressed in vascular endothelial cells (VECs) and has a remarkable role in the regulation of expression of specific genes in VECs (7).

Previous studies indicated that miR-24 has a major role in the regulation of VECs functions as proliferation, differentiation, angiogenesis, apoptosis, and inflammation. The dysregulated expression pattern of miR-24 is associated with dysfunction or even damage of VECs and leads to the occurrence of cardiovascular diseases (8).

YKL-40, recognized as chitinase 3-like 1, is an inflammatory glycoprotein mainly secreted by endothelial cells, activated macrophages, neutrophils, in addition to chondrocytes and synovial cells (9). This protein participates in many influential biological processes, such as proliferation, inflammation, angiogenesis, and tissues rebuilding (10).

YKL-40 is implicated in the pathogenesis of endothelial dysfunction and thereby atherosclerosis by affecting chemotaxis, cell adherence, migration, and finally reorganization as a reaction to endothelial injury (11). In the study done by Roslind et al., 2009, they introduced YKL-40 as a biomarker for angiogenesis and extracellular matrix degeneration due to its crucial role in inflammation (12).

The study done by Shao et al., 2009 made insight on the angiogenic signature of YKL-40 in the pathogenesis of a wide range of human cancers in addition to inflammatory diseases. They stated that the mechanism of action of YKL-40 in inducing angiogenesis involves the co-activation of membrane receptor syndecan-1 (SDC-1) and downstream signaling effectors as focal adhesion kinase (FAK) and mitogen-activated protein (MAP) Kinase in endothelial cells (13).

Deng et al. (2017) declared a novel mechanism of miR-24 regulating its target YKL-40 expression by directly binding to the YKL-40 mRNA 3′ UTR seed sequence (14).

The results of the research conducted until now have encouraged our group to evaluate the possible role of miR-24 and its target YKL-40 in the pathogenesis of the CVS morbidity associated with SLE as evidenced by the presence of endothelial dysfunction with atherosclerosis ensued.

Materials and Methods

Study design & population

This is a cross sectional observational study, conducted on forty SLE patients and forty age and sex-matched healthy subjects served as controls. SLE patients were fulfilling the criteria of the 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification (15).

SLE disease activity was assessed according to the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). Hence, the patients were divided according to their SLEDAI scores into patients with SLEDAI score of >10 (active SLE) and patients with SLEDAI score of ≤10 (inactive SLE).

The study subjects were classified as follows:

Group 1: Forty age and sex matched-healthy controls (33.3%) with no history of autoimmune diseases and their ages ranged from (19-47 Years), 70% of this group was females.

Group 2: Forty SLE patients (66.7%), they were 92.5% females and 7.5% males with ages ranged from (14-51 Years).

It is worthy mentioned that patients with other autoimmune or cardiovascular diseases were excluded in addition to diabetic and hypertensive patients and those with cancer or concurrent infections.

SLE patients of our study were recruited from Internal Medicine Department, Kasr Al Ainy Hospital, Cairo University during the period of (Feb 2020 to Oct 2020). The study protocol was promoted to the ethical guidelines of the Helsinki declaration 1975 and was reviewed & agreed by the ethical committee of Faculty of Medicine, Cairo University. Informed written consents were taken from all subjects enrolled in this study.

Routine laboratory measures

All laboratory measurements used to determine SLEDAI scores were performed in the central lab of Kasr Al Ainy Hospital, Cairo University, using standard quality control measures. These laboratory parameters included determination of serum levels of C3, C4, creatinine and anti–double-stranded DNA (anti-dsDNA), complete blood cell counts, erythrocyte sedimentation rate (ESR), and urinary levels of protein and creatinine.

Blood sample collection and storage

Peripheral blood sample was withdrawn from each subject and taken in plain tube for centrifugation and serum separation. Then, serum was stored at −80 °C for micro-RNA extraction and detection of the fold change of miR-24 gene as well as RNA extraction and quantification of SDC-1 mRNA using real time PCR. In addition, the serum was utilized for estimation of serum level of the study parameters (YKL-40 and Vascular cell adhesion molecule; VCAM).

Measurement of SDC and miR-24-fold changes: Isolation of total RNA

Total RNA with preserved micro-RNAs was extracted by miRNeasy extraction kit (Qiagen, Valencia, CA, USA) according to the manufacturer's instructions. RNA samples were subjected to RNA quantitation and purity assessment using the NanoDrop® (ND)-1000 spectrophotometer (NanoDrop Technologies, Inc. Wilmington, USA). The extracted RNA was then stored at -80 °C for later use.

Reverse transcription (RT) and real-time quantitative PCR (qPCR)

According to the manufacturer's protocol using the miScript II RT kit (Qiagen, Valencia, CA, USA), extracted RNA (1 µg) was reverse transcribed to cDNA in a final volume of 20 µL RT reactions and were incubated for 60 min at 37 °C, followed by 5 min at 95 °C.

Real-time qPCR was done according to the Manufacturer's recommendations using miScript SYBR Green PCR kit (Qiagen, Valencia, CA, USA) that included miRNA- 24 specific forward primer (5'-TTCTCCGGGCTGTCGATTGG-3') and its reverse primer (5'-CAAGGGCTCGACTCCTGTTC-3') in addition to U6 as an internal reference (5'GCTTCGGCAGCACATATACTAAAAT 3'/ 5' CGCTTCACGAATTTGCGTGTCAT3'). To detect and estimate the mRNA expression of SDC-1 gene, SDC-1 related forward and reverse primers respectively (5' TCTGACAACTTCTCCGGCTC 3' / 5'CCACTTCTGGCAGGACTACA 3') were used beside B-actin housekeeping gene as an internal control (5'GTGGGCCGCACAAGGCACCAA 3'/ 5'CTCTTTGATGTCACGCACGA 3').

20 ng of cDNA were used as a template in a total volume of 20 µL reaction with the following conditions: denaturation at 95 °C for 15 min followed by 40 cycles of 94 °C for 15 s, 55 °C for 30 s, and 70 °C for 34 s, in which fluorescence was developed and detected by Rotor-gene Q Real-time PCR system (Qiagen, USA). After the PCR cycles, melting curve analyses were carried out to confirm the specific generation of the expected PCR product. The threshold cycle ($2^{-\Delta\Delta Ct}$) method of comparative PCR was used to interpret the results.

Measurement of serum YKL-40 and VCAM

The concentrations of YKL-40 protein in the serum samples were measured by quantitative double-antibody sandwich enzyme linked immunosorbent assay (ELISA) technique, using commercially available kits (Elabscience, Houston, USA, Catalog number# E-EL-M0016) according to the manufacturer's instructions. The results were calculated by reference to the standard curve and expressed as ng/ml.

Besides, we detected the serum level of VCAM using (MYBIOSOURCE, USA, Catalog number# MBS175995)

Statistical analysis

Data were coded and entered using the GraphPad Prism version 7. Data was summarized using mean and standard deviation for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Comparisons between groups were done using Mann-Whitney test in quantitative variables (R). Correlations were done using Spearman test. P-values less than 0.05 were considered as statistically significant (16).

Results

Demographic and Clinicopathological Data

As previously mentioned, the present study was carried out on eighty subjects classified into 2 groups. Regarding the sex of SLE patients, the male subjects were 3 (7.5%) and the female patients constituted 37 (92.5%) with a mean age of 28.35 ± 7.94 years and disease duration of 3.504 ± 3.828 years. The forty healthy control subjects were of matched age (30.5 ± 9.174 years; P= 0.3519) and sex (31 (70%) females and 9 (30%) males; P=0.11) as shown in (Table 1). The various clinicopathological parameters of SLE patients indulged in this work are shown in (Table 2).

Table 1. Demographic data of the studied groups.

		Control (N=40)	SLE Patients (N=40)	P-value	P value
Age (years)		30.5 ± 9.17	28.35 ± 7.94	0.35	NS
Sex	**Male**	9 (22.5 %)	3 (7.5 %)	0.11	NS
	Female	31 (77.5 %)	37 (92.5 %)*		

Data are expressed as mean ± SD. P-value <0.05 is considered statistically significant.

Table 2. Clinicopathological Parameters in SLE patients.

Variable	SLE patients	Variable	SLE patients
SLEDAI Activity	12.8 ± 11.34	Pleurisy	4 (10 %)
Neuropsychiatric symptoms	8 (20%)	Low complement	19 (47.5%)
Vasculitis	1 (2.5%)	Anti−ds DNA positivity	14 (35%)
Arthritis	20 (50%)	Fever	13 (32.5%)
Hematuria	4 (10%)	Psychosis	5 (12.5%)
Proteinuria	20 (50%)	Anemia	35 (87.5 %)
Alopecia	26 (65%)	Thrombocytopenia	6 (15%)
Oral ulcers	13 (32.5%)	Leucopenia	5 (12.5%)
Malar Rash	11 (27.5%)		

Laboratory Data of Involved Subjects

By comparing different laboratory parameters between the control and SLE studied groups, we found statistical significance regarding Hb (*P*= 0.0002), platelet count (*P* <0.0001), total leucocytic count (*P* <0.0001), ESR (*P*

<0.0001), serum C3 and C4 complements *(P* <0.0001), serum urea (*P*= 0.0021), serum albumin (*P* <0.000) and 24 hours proteinuria *(P*=0.0005*)*. As for the subjects' lipid profiles, remarkable statistical difference was noticed concerning serum cholesterol (*P* <0.0001), triglycerides (*P* <0.0001), LDL (*P* < 0.0001) and HDL (*P*=0.0002) (Table 3).

Table 3. Laboratory variables among the studied groups.

Groups / Variables	Control group (N=40) Mean ± SD	SLE (N=40) Mean ± SD	P-value
Hb (gm/dl)	11.82 ± 1.12	10.21 ± 1.64	0.0002*
Platelet Count	343900 ± 171314	265800 ± 106900	<0.0001*
TLC	7100 ± 2115	6950 ± 3820	<0.0001*
ESR (mml/h)	9.56 ± 2.94	58 ± 34.41	<0.0001*
Serum C3 (mg/dl)	110.6 ± 7.67	76.54 ± 12.78	<0.0001*
Serum C4 (mg/dl)	16.4 ± 2.54	10.1 ± 5.42	<0.0001*
Serum Urea	24.55 ± 9.09	62.1 ± 51.42	0.0021*
Serum Albumin	4.67±0.62	2.98 ± 0.62	<0.0001*
24 hours urinary protein	0.003± 0.002	1.07 ± 1.29	0.0005*
Cholesterol	153.3 ± 14.71	220.2 ± 45.02	<0.0001*
TGs	118.4 ± 18.46	234.6 ± 23.05	<0.0001*
LDL	84.53 ± 18.8	140.7 ± 51.67	<0.0001*
HDL	46.45 ± 7.24	32.55 ± 14.8	0.0002*

P value is considered significant if <0.05.

Circulating miR-24 targeting serum YKL-40 protein

In this study, miR-24-fold change was found to be different with statistical significance between the control and SLE groups (*P =0.0001*). When we compared serum level of YKL-40 protein, it was higher among SLE group than the control subjects with statistical significance (*P=0.0001*) (Table 4).

Table 4. Comparison of the studied parameters between control and SLE groups.

Variables / Groups	Control group (N=40) Mean ± SD	SLE (N=40) Mean ± SD	P-value
miRNA-24	1.027 ± 0.06	0.405 ± 0.24	0.0001*
YKL-40	165.3 ± 47.3	578 ± 67.28	0.0001*
Syndecan	1.024 ± 0.037	6.949 ± 2.738	<0.0001*
VCAM	2.26 ± 0.77	5.865 ± 2.92	0.0001*

P value is considered significant if <0.05.

Pearson's coefficient correlation was done to evaluate the association of circulating miR-24 with YKL-40 level among SLE subjects. miR-24 was significantly and negatively correlated with YKL-40 (*r= -0.85, p= <0.0001*) (Fig. 1).

Plasma levels of biomarkers reflecting endothelial injury

SDC-1 fold change was significantly higher (*p < 0.0001*) in patients with SLE compared to the control group. In addition, when we examined serum level of VCAM protein, it

was found to be higher among SLE group than the control subjects with statistical significance (*P= 0.0001*) (Table 4).

Furthermore, we investigated the correlation between circulating SDC-1 fold change and serum VCAM level and we got significant positive correlation (*r= 0.35, P= 0.02*) (Fig. 2).

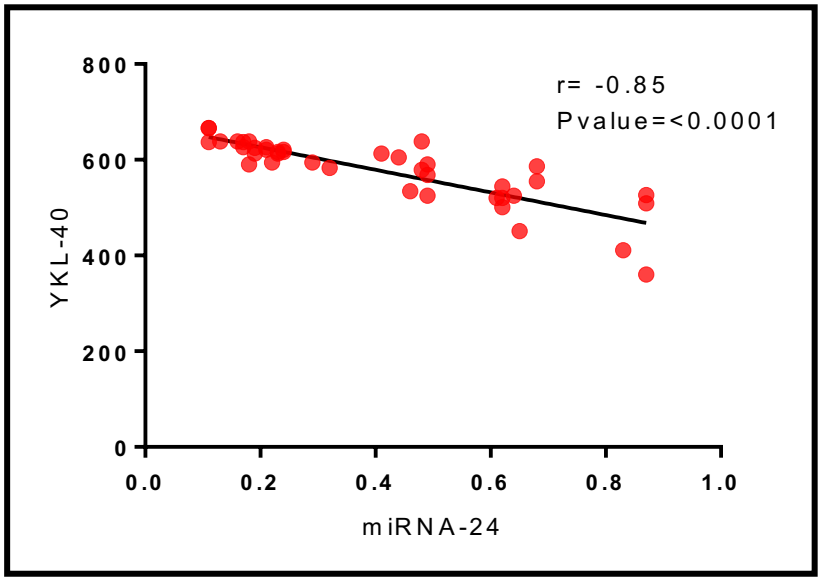

Fig. 1. Correlation between circulating miR-24 and serum YKL-40 among SLE patients.

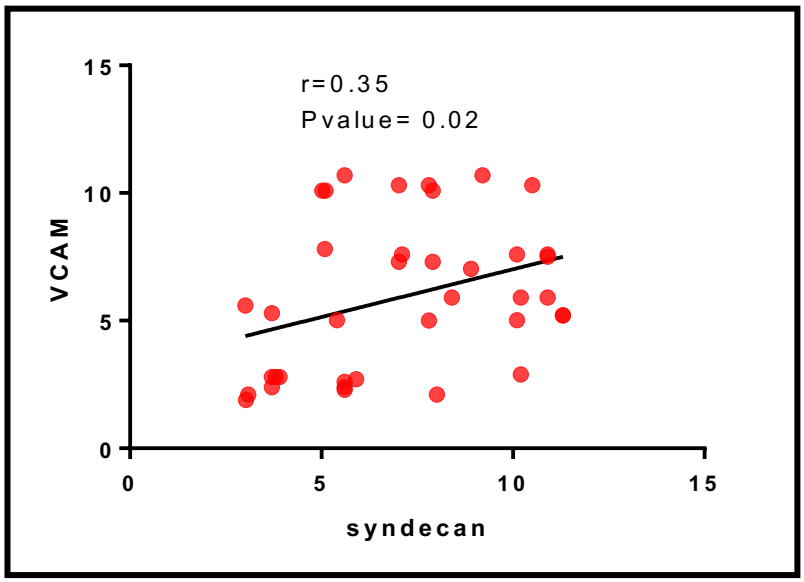

Fig. 2. Correlation between circulating SDC-1 Fold Change and serum VCAM among SLE patients.

Assessment of the role of the measured parameters in the pathogenesis of CVS complications in SLE

In this context, we noted that miR-24-fold change was significantly and negatively correlated with SDC-1 fold change (*r= -0.744, P < 0.0001*) (Fig. 3). Besides, we got remarkable and negative association between miR-24-fold change and serum level of VCAM among SLE group (*r= -0.42, P= 0.006*) (Fig. 4).

As for serum YKL-40 protein, it was significantly and positively associated with both SDC-1 fold change (*r= 0.6404, P= <0.0001*) (Fig. 5), serum VCAM level (*r= 0.3897, P= 0.0129*) (Fig. 6).

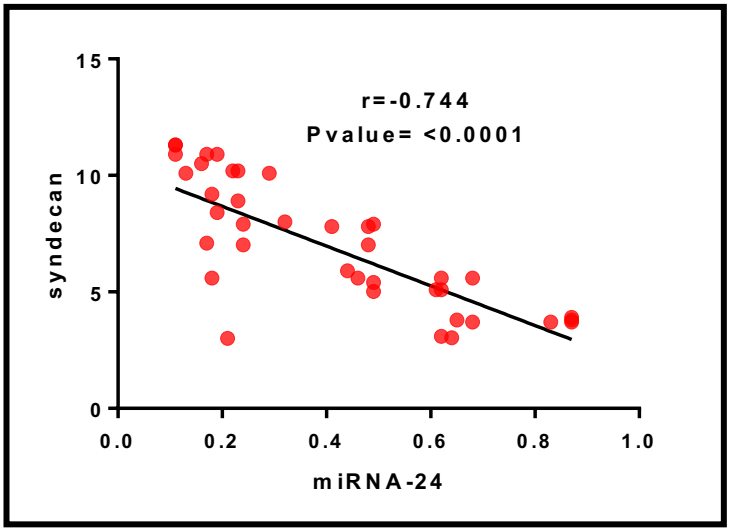

Fig. 3. Correlation between the Fold Changes of miR-24 and SDC-1 in SLE group.

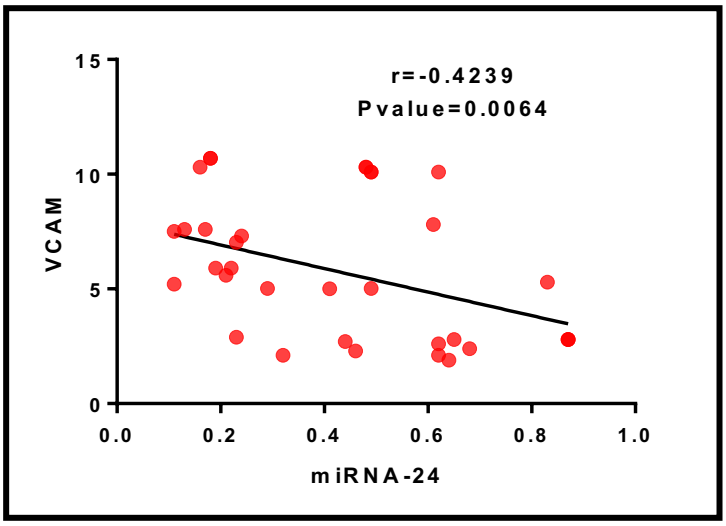

Fig. 4. Correlation between the Fold Change of miR-24 and serum VCAM level in SLE group.

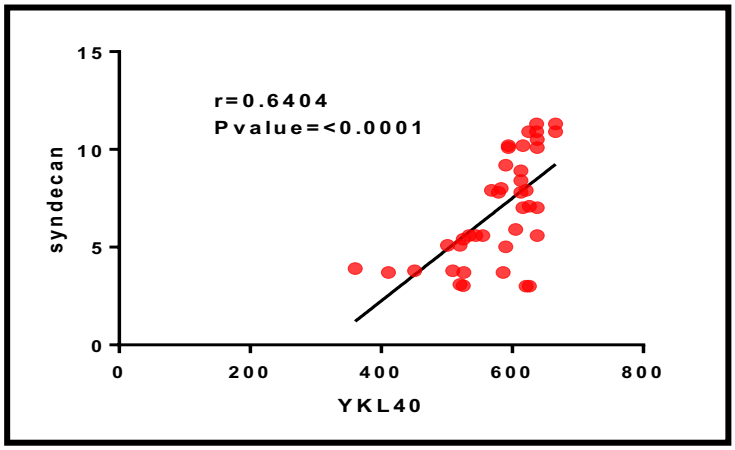

Fig. 5. Correlation between serum YKL-40 protein level and SDC-1 Fold Change in SLE group.

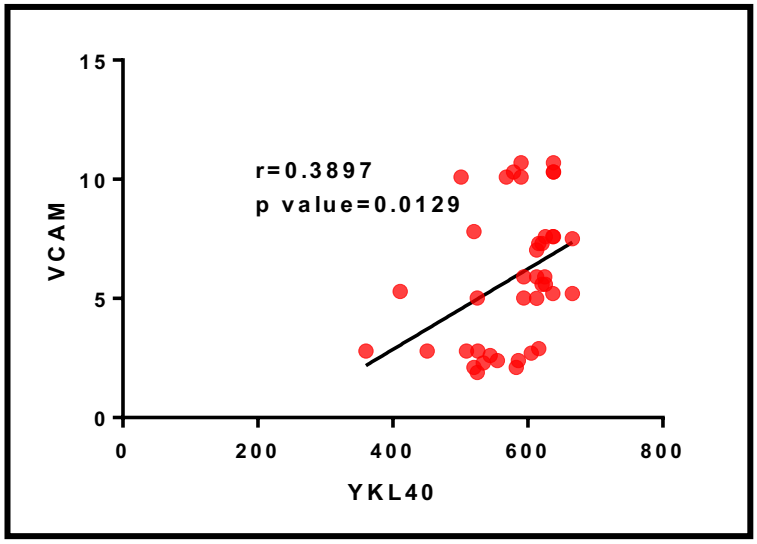

Fig. 6. Correlation between serum levels of YKL-40 protein and VCAM in SLE group.

We evaluated the correlation between the study parameters and the biochemical markers for atherosclerosis i.e., LDL, Cholesterol, and HDL (Table 1). We got significant and negative correlation between miR-24-fold change and serum LDL (*r= -0.65*) and cholesterol (*r= -0.62*) (*P<0.0001 for each*). Conversely, miR-24 and serum HDL were significantly and positively correlated (*r= 0.38, P= 0.01*).

As for serum YKL-40 protein level, it was noticeably and positively associated with serum levels of LDL (*r= 0.56, P= 0.0002*) and cholesterol (*r= 0.52, P=0.0006*). Reversibly, serum YKL-40 was significantly and negatively correlated with serum HDL (*r= -0.36, P= 0.02*) (Table 5).

Table 5. Correlation between the study parameters and SLE patients' Lipid Profiles.

Variables \ Groups	LDL	Cholesterol	HDL
miRNA-24	r= -0.65	r= -0.62	r= 0.38
	P= <0.0001	P= <0.0001	P= 0.01
YKL-40	r= 0.56	r= 0.52	r= - 0.36
	P= 0.0002	P= 0.0006	P= 0.02
Syndecan-1	r= 0.5	r= 0.53	r= - 0.14
	P= 0.001	P= 0.0004	P= 0.4

P value is considered significant if <0.05.

Regarding SDC-1 fold change, it was remarkably and positively correlated with serum LDL (*r= 0.5, P= 0.001*) and cholesterol (*r= 0.53, P= 0.0004*). Unlike miR-24-fold change and serum YKL-40, no significant correlation was detected between SDC-1 fold change and serum HDL (*r= -0.14, P=0.4*) (Table 5).

It is worthy mentioned that none of the measured parameters were found to be significantly correlated with the demographic neither the clinic-pathological variables of the studied subjects.

Discussion

SLE is a chronic autoimmune disease in which autoantibodies are produced resulting in the formation of immune complexes which are deposited in various organs affecting them dramatically (17).

SLE is correlated with an increased risk of cardiovascular morbidity and mortality (18). Classical risk factors like hypertension, dyslipidemia, sex, age, smoking and obesity in

addition to SLE-specific and treatment-related factors all result in increased risk of cardiovascular disease. However, the pattern of risk factors causing the excess occurrence of cardiovascular disease in SLE is incompletely identified (19).

Accelerated atherosclerosis is considered a general feature of SLE and is assumed to be the main cause of premature CVD. Atherosclerosis occurs prematurely in SLE patients and is independent of traditional risk factors for CVD. The occurrence of accelerated atherosclerosis was supported by several studies (20).

The present study aimed to investigate whether miR-24 through targeting YKL-40 is implicated in the pathogenesis of endothelial dysfunction and thereby atherosclerosis event seen in SLE patients or not.

In the present study, we reported a significant reduction in the expression level of circulating miR- 24 in SLE patients compared to the control subjects. This result is in concordance to the finding shown by Murata et al (2013) who through comprehensive microRNA analysis revealed that the level of miR-24 in SLE patients was lower than that in RA (21). This outcome could be attributed to the anti-inflammatory action of miR-24 which supported by previous studies that demonstrated miR-24 exerts its anti-inflammatory action by inhibition of the production of pro-inflammatory cytokines in lipopolysaccharide -stimulated macrophages (22,23).

SLE patients enrolled in the present study showed a significantly higher serum level of YKL-40 protein compared to the control. This result came in agreement with Wcisło-Dziadecka et al. (24) that observed significant increase in serum YKL-40 protein in SLE patients. They also, suggested that increased serum YKL-40 protein in SLE patients results mainly from inflammation. Former studies (25-27) showed that serum levels of YKL-40 protein are increased in chronic inflammatory conditions such as SLE, inflammatory bowel disease and sarcoidosis. A previous study suggested a role for YKL-40 in triggering inflammation and smooth muscle cells' migration through increasing IL-8 production via mitogen-activated protein kinase (MAPK) and NF-κB pathways (28).

Also, in the present study, circulating miR-24 was significantly and negatively correlated with YKL-40 among SLE patients, as determined using Pearson's correlation analysis. This result was shown in former studies but in other diseases. Deng et al. (14) reported that reduced level of miR-24 is associated with elevated levels of YKL-40 in type 2 diabetes mellitus patients with coronary heart diseases. Besides, they described a novel regulatory mechanism of miR-24 regulating its target YKL-40 expression by directly adhering to the YKL-40 mRNA 3′ UTR seed sequence. In agreement with these findings, another study found that the expression of miR-24 was significantly down-regulated in osteomyelitis patients, and it demonstrated that overexpression of miR-24 suppressed the expression of YKL-40 mRNA, by directly binding to the 3'-untranslated region (29).

SDC-1 is one of the four subtypes of Syndecans which belong to the heparin-sulfate proteoglycan family and play multiple roles in various biological processes including inflammation and wound healing (30). SDC-1 is mostly expressed on the surface of plasma cells, endothelial cells, and epithelial cells. Under certain pathological circumstances, the ecto-domain of SDC-1 can be shed from the cell surface and released into extracellular fluid (30). Released SDC-1 into plasma will remain active influencing the behavior of plasma cells, derived from B cells. This induces the plasma cells to produce pathogenic auto antibodies in SLE; leading to the suggestion that SDC-1 probably has a pathogenic role in this autoimmune disease (31). In the current study, SDC-1 mRNA was measured and found to be significantly higher in patients with SLE compared to the control group. This agreed with the result demonstrated by former studies that included SLE patients (32,33). This similarity, among different studies, strengths the reasonable role of SDC-1 in the pathogenesis of SLE.

Previous studies revealed elevated levels of cell adhesion molecules in SLE patients. It is worthy mentioned that these adhesion molecules allow leukocyte adhesion and rolling along the surfaces of endothelial cells in addition to leading the migration of leukocytes into inflamed tissues. These molecules ease, through chemokines and chemo-attractants, leukocyte–endothelial cell interactions and inflammatory cells transmigration to sites of inflammation thereby acting as markers of endothelial activation and dysfunction (34,35). Among these cell adhesion molecules is VCAM-1 which in our study was higher among SLE patients than in our control group. This finding corroborates the results of previous studies that showed that VCAM-1was significantly higher in SLE patients than in controls (36-38).

The present study demonstrated significant positive correlation between serum YKL-40 protein and SDC-1 fold change. Shao R. (2013) found that YKL-40 stimulates the coupling of membrane-bound syndecan-1 with an adjacent membrane-associated protein integrin αvβ5, resulting in downstream activation of focal adhesion kinase 397 (FAK397) and mitogen-activated protein kinases (MAPK) 1 and 2, thereby up-regulating vascular endothelial growth factor (VEGF) gene expression, which in turn collaborates with YKL-40 to activate endothelial cells and trigger angiogenesis (39). It is worthy mentioned that neovascularization in atherosclerotic lesions has a considerable role in plaque growth and instability. Besides, it may take part in plaque destabilization and thromboembolic complications (40).

A major finding of this study is that SDC-1 fold change was found to be significantly and positively correlated with serum VCAM among SLE patients. Till now, up to our knowledge, such association hasn't been demonstrated before in SLE. This finding is consistent with the results of previous studies which showed that SDC-1, through autoantibodies formation, (31) and the up-regulation of adhesion molecules including VCAM are indulged in SLE pathogenesis (41). In addition, this correlation could be explained by the data of former work that showed that SDC-1 is involved in the up-regulation of vascular endothelial growth factor (VEGF) (39), which in turn increases the endothelial permeability and induces the formation of adhesion molecules (including VCAM) that bind leukocytes to endothelial cells triggering angiogenesis and inflammation which are characteristic features of SLE (42,43).

It is well known that inflammation has a key role both in the development of the atherosclerotic lesion, and, in the acute rupture of plaques that occurs during acute myocardial ischemia. During the development of SLE, the interplay of multiple inflammatory mediators, including leukocytes, cytokines, chemokines, adhesion molecules and auto- antibodies, results in the formation of atherosclerotic plaques (44). All these data led us to question about the role of miR-24 altered expression through its target YKL-40 protein in inducing inflammation and thereby atherosclerosis among SLE subjects. Our study revealed remarkable and negative association between miR-24-fold change and serum VCAM level. Besides, miR-24-fold change was significantly and negatively correlated with serum cholesterol. The latter was positively correlated in significance with serum VCAM. This finding came in line with former study that showed that cholesterol exposure or accumulation within the endothelial cells is critical for VCAM-1 expression and by this pathway, high blood LDL or cholesterol levels can create a proinflammatory and proatherogenic state (45). Furthermore, it was reported that increased levels of VCAM-1 and other adhesion molecules are associated with inflammation, dyslipidemia, and cardiovascular events (46).

In conclusion, the current study described a possible pathway for the increased risk of atherosclerosis occurred in SLE. Reduced miR-24-fold change was accompanied with increased serum YKL-40 protein level. This results in increased SDC-1 fold change with its impact on serum VCAM which appeared to be

also, elevated. All these results were associated with what is known as “lupus pattern of dyslipoproteinemia “where SLE subjects showed elevated triglycerides, LDL, and cholesterol in addition to decreased HDL. This work provided an insight into the role of miR-24 and its target serum YKL-40 protein in the development of SLE-related inflammation and atherosclerosis.

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