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ORIGINAL ARTICLE

Clinical significance of lipid profile in systemic lupus erythematosus patients: Relation to disease activity and therapeutic potential of drugs

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Abstract *Aim of the work:* To study the lipid profile in systemic lupus erythematosus (SLE) patients and correlate it with disease activity parameters. The effect of hydroxychloroquine (HCQ), steroids and azathioprine on the lipid profile was also determined.

Patients and methods: The study included 48 female SLE patients. Total cholesterol, triglycerides and high density lipoprotein cholesterol (HDL-C) were measured in plasma. Low density lipoprotein cholesterol (LDL-C) and very low density lipoprotein cholesterol (VLDL) were calculated. Disease activity was assessed using the systemic lupus activity measure (SLAM).

Results: The mean age of the patients was 25.7 ± 7 years. Hypercholesterolemia was present in 23 (47.9%) patients and hypertriglyceridemia in 16 (33.3%). There was no significant difference in the lipid profile of SLE patients receiving 200 or 400 mg/day HCQ. No significant difference in the lipid profile was found among patients who did not receive steroids, those who received 10 mg/day and those who received >10 mg/day. A significant difference in cholesterol and LDL-C level was present between SLE patients with (243.1 ± 84.3 mg/dl and 166.1 ± 65.7 mg/dl) and without (192.7 ± 50.6 mg/dl and 115.7 ± 44.4 mg/dl) lupus nephritis (LN) ($p = 0.01$, $p = 0.002$ respectively). SLAM significantly correlated with triglycerides and VLDL and negatively with HCQ intake ($r = -0.3$, $p = 0.04$).

Conclusion: Disease activity of SLE patients affects the lipid level and its control can be helpful in treatment strategies. The use of HCQ through its reduction of disease activity added to low dose steroids may reduce the lipid profile of SLE patients. Control of hyerlipidemia can favourably affect SLE renal disease.

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1. Introduction

The improvement in survival rates of SLE patients has led to the recognition of premature atherosclerosis as an important cause of coronary artery disease in these patients. One of the important traditional factors contributing to premature atherosclerosis is dyslipoproteinemia [1,2]. This dyslipoproteinemia ranges between 30% and 73% of the adult SLE patients. Studies have shown that there are two patterns of dyslipoproteinemia [3–5]. The first is related to active disease where there are increased levels of triglycerides and high density lipoprotein (HDL) [6], while the second is related to high dose steroid therapy and not related to active disease [7,8]. Actually it is difficult to differentiate between the two patterns and there are no clear distinctive boundaries between them.

It has been shown that there is an association between elevated levels of triglycerides, small dense low density lipoprotein-cholesterol (LDL-C), low levels of HDL-C and atherosclerosis. Steroid therapy has been shown to alter lipid levels [9]. The administration of antimalarial drugs in SLE patients not only treats constitutional symptoms and mild to moderate organ involvement but it has lipid lowering properties. This is attributed to a decrease in cholesterol synthesis, inhibition of lysosomal hydrolysis, increased uptake of LDL and alterations in insulin resistance [10–13]. Antimalarials are particularly effective in reducing VLDL which is the lipid part affected by steroids. Therefore antimalarials are more efficient in reducing cholesterol levels in the presence of steroids [7].

The aim of the present study was to reveal the changes and clinical significance of the lipid profile in SLE patients and to correlate it with the disease activity parameters. Another aim was to study the effect of hydroxychloroquine (HCQ), steroid and azathioprine therapy on the lipid profile level.

2. Patients and methods

The present study included forty-eight female SLE patients attending the Rheumatology and Rehabilitation outpatient clinic of Cairo University Hospitals between September 2013 and July 2014. The patients fulfilled the updated American College of Rheumatology (ACR) revised criteria for the classification of SLE [14]. The patients had a mean age of 25.7 ± 7 years and a mean disease duration of 5.9 ± 4.8 years. The patients underwent full history taking and clinical examination including cardiopulmonary, neurological, gastrointestinal, renal, musculoskeletal and dermatologic examination. The protocol of the research was approved by the institution within which the work was undertaken and it conforms to the provisions of the world association's Declaration of Helsinki. All patients gave informed consent. Exclusion criteria included menopausal women and hypothyroidism. None of the patients received lipid lowering drugs, estrogen and progesterone containing agents or thyroid medication at the time of study or three months prior to it [15]. None of the patients were smokers or alcoholics.

Laboratory tests performed to the patients included complete blood count, erythrocyte sedimentation rate (ESR), liver function tests including aspartate aminotransferase (AST) and alanine aminotransferase (ALT), kidney function tests including blood urea nitrogen, serum creatinine and creatinine clearance as well as complete urine analysis. Antinuclear antibodies (ANA) and anti-deoxyribonucleic acid antibodies (anti-DNA) were performed by immunofluorescence and complement (C3 and C4) by radial immunodiffusion. Lipid profile was measured after an overnight fasting. Total cholesterol (TC) and triglycerides (TG) were measured by the calorimetric method using commercial assays. High density lipoprotein cholesterol (HDL-C) was measured using the direct HDL method (Hitachi 917) [16]. Low density lipoprotein cholesterol (LDL-C) was calculated using the formula LDL-C = TC–(TG/2.2 + HDL-C). Very low density lipoprotein cholesterol (VLDL) was calculated by multiplying TG by 0.45 [16]. Cholesterol levels were considered to be normal at less or equal to 200 mg/dl, triglycerides at less or equal to 150 mg/dl, HDL-C at more than or equal to 50 mg/dl and LDL-C at less or equal to 130 mg/dl [17]. Disease activity was assessed using the systemic lupus activity measure (SLAM) [18].

Chest X-ray, computed tomography of chest and echocardiography were performed for suspected cases of pleurisy, interstitial pulmonary fibrosis and pancarditis. Renal biopsy was performed for those cases of suspected lupus nephritis based on laboratory and clinical data.

All the patients were on oral steroids except for four patients at the time of the study, 15 patients were on a dose of 10 mg/day and 29 patients took more than 10 mg/day. The mean steroid dose was 15.8 ± 8.6 mg/day with a mean duration of 3 ± 2.7 years. Twenty-one patients did not receive antimalarials. Twenty-seven patients received hydroxychloroquine (HCQ) with a mean dose of 183.3 ± 179 mg/day and a mean duration of intake of 2.7 ± 2.76 years. Ten of these patients received a dose of 200 mg/day of HCQ with a mean duration of intake of 3.71 ± 3.41 years and 17 patients received 400 mg/day with a mean duration of intake of 2.18 ± 2.35 years. Twenty patients received azathioprine with a mean dose of 97.5 ± 30.24 mg/day and a mean duration of intake of 2.79 ± 2.62 years. Five patients received pulse cyclophosphamide monthly infusions of 0.5-1 g/m^2 for 6 months for lupus nephritis and vasculitis but all had finished the infusions at least 3 months prior to entry in the study. In this study, 4 patients did not receive any medications, 1 received HCQ only, 11 patients took only prednisolone, 13 patients received prednisolone + HCQ, 13 patients took prednisolone + HCQ + azathioprine (AZA) and 7 patients took prednisolone + AZA.

Statistical analysis: Data were recorded and analyzed using the statistical package SPSS version 12. Data were expressed as mean ± standard deviation. Comparison between 2 groups was by Student's *t*-test and more than two groups by analysis of variance (ANOVA). Correlation was done by Pearson's correlation coefficient. *P* values less than 0.05 were considered statistically significant.

3. Results

The study included 48 adult SLE female patients with an age range between 17 and 45 years and a mean of 25.7 ± 7 years. The disease duration ranged between 2 months and 18 years with a mean of 5.9 ± 4.8 years. Systolic blood pressure ranged between 100 and 200 mmHg with a mean of 133.5 ± 25 mmHg and diastolic blood pressure ranged between 60 and 150 mmHg with a mean of 88 ± 17 mmHg. SLAM score

ranged between 3 and 23 with a mean of 11 ± 4.5. The mean hemoglobin level was 10.4 ± 1.7 g/dl, the mean erythrocyte sedimentation rate (ESR) in the 1st hour was 69 ± 38 mm/hour and the mean platelet count was 318 ± 153 × 10^3/mm^3. The mean C3 was 0.74 ± 0.38 g/l and the mean C4 was 0.14 ± 0.12 g/l.

Hematologic manifestations were the most prevalent occurring in 33 patients (68.75%) followed by arthritis occurring in 27 patients (56.25%). Eleven patients (22.9%) had a rash whether malar or maculopapular and 15 patients (31.25%) had Raynaud's phenomenon. Lupus nephritis was present in 22 patients (45.8%). Pleural effusion and pleurisy was present in 15 patients (31.25%) and carditis in 6 (12.5%). Central nervous system (CNS) manifestations were present in the form of stroke in 3 patients (6.25%), seizures in 3 (6.25%), cranial nerve palsy in 2 (4.2%) and psychosis in 2 (4.2%). Vasculitis was present in 6 patients (12.5%).

The lipid profile of the SLE patients is shown in Table 1. Hypercholesterolemia was present in 23 (47.9%) patients and hypertriglyceridemia in 16 (33.3%).15 patients had a cholesterol level above 240 mg/dl. Table 2 shows the lipid profile of those patients who did not receive any antimalarials (21 patients) and those who received 200 mg/day (10 patients) and 400 mg/day of HCQ (17 patients). There was no significant difference between the 3 groups. A comparison was made regarding the lipid profile of those who did not take steroids (4 patients), those who received 10 mg/day (15 patients) and those who received more than 10 mg/day (29 patients). Also there was no significant difference between the 3 groups (Table 3). Table 4 makes a comparison regarding the lipid profile among the patients who did not receive AZA (28 patients) and those who received the medication (20 patients). Also the difference was not statistically significant.

Comparison between SLE patients with (22 patients) and without nephritis (26 patients) as regards the lipid profile showed only significant differences in the cholesterol level and the LDL-C level (Table 5). While comparison of the lipid profile between the SLE patients with CNS (10 patients) and without CNS manifestations (38 patients) did not show any statistically significant differences (Table 6).

Correlation of the various lipid profile parameters was done with a few disease activity parameters. Triglycerides and VLDL cholesterol showed a significant correlation with the SLAM index ($p = 0.04$ for both). There was no significant correlation between the lipid profile subfractions and ESR, C3, C4 or platelet count (Table 7). There was a significant negative correlation between HCQ dose and SLAM ($r = -0.297$, $p = 0.04$) (not shown in the tables).

Table 1 The lipid profile of the SLE patients.

Lipid profile Mean ± SD (range)	SLE patients ($n = 48$)	
TC (mg/dl)	212.2 ± 73.9	(69–447)
HDL-C (mg/dl)	40.02 ± 11.2	(17–98)
LDL-C (mg/dl)	137.6 ± 59.6	(43.2–321.4)
TG (mg/dl)	169.6 ± 79.9	(56–383)
VLDL (mg/dl)	80.3 ± 42.3	(25.2–242.1)

TC: total cholesterol; HDL-C: high density lipoprotein-cholesterol; LDL-C: low density lipoprotein-cholesterol; TG: triglycerides; VLDL: very low density lipoprotein-cholesterol.

4. Discussion

Reports in the literature of premature atherosclerosis in SLE patients have been attributed to traditional risk factors as well as to the disease process itself and to its treatment [19,20]. One of these traditional risk factors is dyslipidemia which is a common finding in SLE [21].

In the present study we reported hypercholesterolemia (>200 mg/dl) in 23 patients (47.9%), 15 of these patients had a cholesterol level >240 mg/dl. Hypercholestrolemia's prevalence varies between the different studies. Manzi and his colleagues reported a 5.4% prevalence as he chose >240 mg/dl as his upper limit [1]. While Bruce et al. reported a prevalence of 33.6% and this difference between our study and his is most probably related to ethnic variations and lifestyle factors [22]. The result was in accordance to that of a study on 221 Egyptian SLE patients showing hypercholesterolemia in 51.1% [23].

The present study shows that the cholesterol, LDL-C, HDL-C, triglycerides and the VLDL cholesterol levels were reduced in patients receiving HCQ compared to those not receiving the drug. The values were not statistically significant and the 400 mg/day dose was not more efficient in lowering the lipid profile than the 200 mg/day dose. In agreement with our results were those of Rossoni et al. [24] and Tam et al. [25] who showed that the lipid profile did not differ among users and non-users of chloroquine. Other authors have reported the beneficial decrease of cholesterol, triglycerides, LDL-C and VLDL cholesterol levels after antimalarial treatment whether chloroquine or HCQ [6,15,26,27]. These differences in our results and other authors can be attributed to our small number of patients and to other factors such as the disease duration, duration of intake of antimalarials and the concomitant use of other medications.

Our results showed that all the lipid profile values were higher in the patients taking more than 10 mg prednisone/day than those receiving 10 mg/day but these values were not higher than those not receiving any prednisone. We were consistent with the results of Sarkissian et al. [28] regarding the cholesterol and the LDL-C levels but we were different regarding the HDL-C levels which they demonstrated were higher in patients receiving prednisone compared to those not receiving the drug. This discrepancy can be due to the fact that decreased HDL-C is associated with active disease and those receiving high dose prednisone were those with active disease. Svenungsson et al. [6] have also commented on this association between low HDL-C levels and active SLE. Our results are also in accordance with Petri and his colleagues who showed that low daily prednisone doses do not significantly affect the lipid profile. In fact they showed that for each 10 mg increase in prednisone dose there was a 7.5 ± 1.46 mg% increase in cholesterol level [7].

In this study there was no difference in the lipid profile between those patients who received AZA and those who did not receive the drug. This is consistent with the results of Rho and his colleagues who showed no difference in the lipid profile among SLE patients who received the drug versus those

Table 2 The lipid profile of the SLE patients according to hydroxychloroquine intake.

Lipid profile Mean ± SD	SLE patients according to HCQ intake and dose (n = 48)			
	No HCQ (n = 21)	200 mg/day (n = 10)	400 mg/day (n = 17)	P
TC (mg/dl)	227.1 ± 82.5	206.1 ± 77.6	206.5 ± 54.5	0.63
HDL-C (mg/dl)	41.8 ± 16.4	39.3 ± 7.96	38.6 ± 3.8	0.69
LDL-C (mg/dl)	125.7 ± 53.5	133.5 ± 68.7	136.4 ± 49.9	0.84
TG (mg/dl)	184.4 ± 91.4	166.4 ± 79.5	157.7 ± 65.6	0.6
VLDL (mg/dl)	91.2 ± 53.5	74.99 ± 35.9	70.9 ± 29.5	0.33

TC: total cholesterol; HDL-C: high density lipoprotein-cholesterol; LDL-C: low density lipoprotein-cholesterol; TG: triglycerides; VLDL: very low density lipoprotein-cholesterol; HCQ: hydroxychloroquine.

Table 3 The lipid profile of the SLE patients according to oral prednisone intake.

Lipid profile Mean ± SD	SLE patients according to prednisone intake and dose (n = 48)			
	No use (n = 4)	10 mg/day (n = 15)	> 10 mg/day (n = 29)	P
TC (mg/dl)	240.3 ± 48.4	187.7 ± 65.6	220.9 ± 79.1	0.23
HDL-C (mg/dl)	54.3 ± 29.4	37.6 ± 7.4	39.3 ± 7.4	0.32
LDL-C (mg/dl)	137.8 ± 73.2	125.2 ± 51.4	143.8 ± 62.7	0.67
TG (mg/dl)	243.0 ± 57.9	167.8 ± 58	175 ± 110	0.13
VLDL (mg/dl)	109.4 ± 26.0	75.5 ± 26.1	78.8 ± 49.5	0.13

TC: Total Cholesterol; HDL-C: high density lipoprotein-cholesterol; LDL-C: low density lipoprotein-cholesterol; TG: triglycerides; VLDL: very low density lipoprotein-cholesterol.

Table 4 The lipid profile of the SLE patients according to azathioprine intake.

Lipid profile Mean ± SD	SLE patients according to azathioprine intake (n = 48)		
	No use (n = 28)	With AZA intake (n = 20)	P
TC (mg/dl)	214.2 ± 65.5	215.4 ± 78.3	0.48
HDL-C (mg/dl)	40.2 ± 13.4	40.7 ± 6.8	0.45
LDL-C (mg/dl)	130.7 ± 54	142.2 ± 66.4	0.26
TG (mg/dl)	194.6 ± 99.6	162.7 ± 87.3	0.87
VLDL (mg/dl)	87.6 ± 44.8	75.5 ± 26.1	0.87

AZA: azathioprine; TC: total cholesterol; HDL-C: high density lipoprotein-cholesterol; LDL-C: low density lipoprotein-cholesterol; TG: triglycerides; VLDL: very low density lipoprotein-cholesterol.

Table 5 The lipid profile of the SLE patients with and without nephritis.

Lipid profile Mean ± SD	SLE patients (n = 48)		
	Without LN (n = 26)	With LN (n = 22)	P
TC (mg/dl)	192.7 ± 50.6	243.1 ± 84.3	0.01*
HDL-C (mg/dl)	40.2 ± 13.8	39.9 ± 7.0	0.54
LDL-C (mg/dl)	115.7 ± 44.4	166.1 ± 65.7	0.002*
TG (mg/dl)	183.8 ± 76.6	153.5 ± 81.4	0.9
VLDL (mg/dl)	82.7 ± 34.5	73.2 ± 39.3	0.9

TC: total cholesterol; HDL-C: high density lipoprotein-cholesterol; LDL-C: low density lipoprotein cholesterol; TG: triglycerides; VLDL: very low density lipoprotein cholesterol.
* $p < 0.05$.

who did not [29]. As AZA is given concomitantly with steroids with or without HCQ as a steroid sparing agent and in the induction of remission of lupus cases, it is difficult to interpret its effect on lipids. Therefore further studies with follow up of the patients are needed to determine its lipid effect.

The lipid profile of our lupus patients showed that there were significantly higher cholesterol and LDL-C levels in patients with lupus nephritis compared to those without. This is in agreement with several authors who reported that dyslipidemia can hasten renal damage through hyperfiltration injury, glomerulosclerosis and tubulointerstitial injury [30–32]. Tisseverasinghe et al. revealed that hypercholesterolemia was an independent factor that predicted unfavourable renal outcome and mortality [33].

The present study revealed that although SLE patients with CNS manifestations (10 patients) had higher mean cholesterol and LDL-C levels compared to SLE patients without CNS manifestations but the differences were not statistically significant. This is contrary to a study performed by Mikdashi et al. who showed that hypercholestrolemia was more common in SLE patients with ischemic stroke [17]. Probably the difference between our results and this study is due to our small number of patients and that the study had an 8 year follow up of patients which we did not perform.

We found in this study that triglycerides and VLDL cholesterol significantly correlated with SLAM index. Sarkissian et al. revealed similar results showing that triglyceride levels tended to decrease with the corresponding reduction in disease

Table 6 The lipid profile of the SLE patients with and without CNS manifestations.

Lipid profile Mean ± SD	SLE patients (n = 48)		
	Without CNS (n = 38)	With CNS (n = 10)	P
TC (mg/dl)	212.3 ± 74.4	216.6 ± 61.8	0.43
HDL-C (mg/dl)	40.7 ± 11.8	37.9 ± 9.4	0.78
LDL-C (mg/dl)	131.7 ± 61.7	146.5 ± 48.9	0.22
TG (mg/dl)	171.8 ± 77.0	161.9 ± 94.4	0.62
VLDL (mg/dl)	77.9 ± 34.2	72.9 ± 42.5	0.63

TC: total cholesterol; HDL-C: high density lipoprotein-cholesterol; LDL-C: low density lipoprotein-cholesterol; TG: triglycerides; VLDL: very low density lipoprotein-cholesterol.

Table 7 Correlation between lipid profile and disease activity variables in SLE patients.

Lipid profile r (p)	Disease activity variables in SLE patients (n = 48)				
	SLAM	ESR	C3	C4	Pl count
TC	−0.03 (0.84)	−0.05 (0.73)	−0.08 (0.61)	−0.03 (0.84)	0.11 (0.46)
HDL-C	−0.08 (0.61)	−0.06 (0.67)	−0.1 (0.49)	−0.04 (0.81)	0.05 (0.73)
LDL-C	−0.1 (0.49)	−0.12 (0.42)	−0.12 (0.42)	−0.06 (0.67)	0.05 (0.73)
TG	0.3* (0.04)	0.24 (0.1)	−0.14 (0.34)	−0.09 (0.53)	0.002 (0.99)
VLDL	0.3* (0.04)	0.24 (0.1)	−0.14 (0.34)	−0.09 (0.53)	0.002 (0.99)

TC: total cholesterol; HDL-C: high density lipoprotein-cholesterol; LDL-C: low density lipoprotein-cholesterol; TG: triglycerides; VLDL: very low density lipoprotein-cholesterol; SLAM: systemic lupus activity measure; ESR: erythrocyte sedimentation rate; C3 and C4: Complement factor 3 and 4; Pl: platelet.
* $p < 0.05$.

activity as measured by systemic lupus erythematosus disease activity index (SLEDAI) [28]. Several authors also documented the increase of triglycerides and VLDL cholesterol with active SLE and that both lipid subfractions denote continuous inflammatory process and the effect of prednisone treatment [34,35].

Although in the present study there was not a statistically significant difference between SLE patients receiving HCQ treatment and those that did not but there was a significant negative correlation between HCQ treatment and the SLAM index. This can have therapeutic implications as it denotes that administration of HCQ can affect SLE disease activity and consequently the lipid profile of the patients. Also, if this treatment is administered with low dose steroids it can have a beneficial lipid lowering effect.

It is very hard to interpret lipid profile results as there are multiple confounding factors such as lifestyle factors, medications and comorbidities that can develop during the course of the disease. We can draw broad observations from this study as the number of patients was small to give conclusive evidence. We deduce that HCQ through its effect on disease activity of SLE patients when administered with low dose steroids may reduce even to a small extent cholesterol, triglyceride, LDL-C and VLDL levels. Proper treatment of hypercholesterolemia should be tackled promptly to avoid the poor renal outcome which it imposes on SLE patients.

Conflict of interest

None.

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