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Association between Abnormal Lipid Levels and Systemic Lupus Erythematosus

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Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that involves vital organs of the body. Studies have shown that abnormal lipids may be involved in the pathogenesis of SLE. Hence, the aim of this study was to evaluate lipid profiles in lupus patients. This retrospective cross-sectional study evaluated 136 SLE patients who were referred to the Rheumatology Clinic of Rafsanjan from October 2015 to September 2018. The data for the SLE disease activity index (SLEDAI) and demographic information of all patients were entered in a researcher-created checklist, and serum lipid profiles were measured in serum samples. The SLEDAI score of patients was 13.8 ± 5.9. Age had a significantly positive correlation with cholesterol ($r = 0.224$, *p value* = 0.009) and LDL ($r = 0.256$, *p value* = 0.003) levels as well as significantly negative correlation with HDL levels ($r = -0.489$, *p value* = 0.023). Lipid profiles of patients with different levels of education showed no significant difference (*p value* = 0.174). In recently diagnosed patients, SLEDAI had a significantly positive correlation with cholesterol ($r = 0.489$, *p value* = 0.002) and LDL levels ($r = 0.418$, *p value* = 0.009) as well as a significantly negative correlation with HDL levels ($r = -0.381$, *p value* = 0.037). No significant correlation was observed between TG level and SLEDAI (*p value* = 0.114, $r = 0.19$). There was no significant difference in the SLEDAI score between subjects using lipid-lowering drugs and those without such treatment (*p value* = 0841). It seems that abnormal lipid levels are common in patients with SLE, and there is an association between abnormal lipids and SLEDAI.

Keywords: Cholesterol, Inflammation, Lipid, Systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that affects multiple organs at different times and causes extensive damage to connective tissue, blood vessels, and serous membranes. This inflammatory disease may affect the skin, joints, blood, kidneys, the central nervous system, or any part of the body. This disease has a wide geographical distribution in different parts of the world, and many differences exist between different ethnic and geographical groups [1]. According to the holistic study of rheumatic diseases conducted by the Center for Rheumatology Research, the prevalence of SLE in Iran is estimated to be 40 cases per 100,000 people [2]. Clinical manifestations and mortality are due to tissue degradation caused by the disease itself or to complications of various drugs for the treatment of lupus [3, 4]. SLE is diagnosed based on clinical and autoantibody manifest-

ations using the European Alliance of Associations for Rheumatology (EULAR)/American College of Rheumatology (ACR) criteria. Involvement of vital organs is one of the characteristics of the disease, due to which the biochemical balance of the blood is disrupted [5]. Dyslipoproteinaemia in SLE involves increased triglycerides (TG) and decreased high-density lipoprotein (HDL), which are closely related to the severity of the disease and can be a measure of heart and kidney disease [6]. Low levels of HDL are related to lupus disease activity. In fact, HDL is a vascular protective agent that stimulates the transfer of cholesterol from the atherosclerotic arteries to the liver, and its anti-inflammatory properties inhibit the adhesion of endothelial cells. It seems that reducing HDL can cause active lupus but may indirectly contribute to increased inflammation in lupus [7]. The prevalence of

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lupus is increasing, and this disease can be life-threatening. Patients suffer from long-term complications of the disease as well as direct and indirect costs resulting from it, which can have a negative impact on the quality of life and daily activities. Therefore, early diagnosis and treatment of this disease are crucial [8]. Despite the fact that studies have already evaluated dyslipoproteinaemia in SLE, research is still limited, and further studies in this field seem necessary. Therefore, the aim of this study was to determine the lipid profiles in lupus patients.

Materials and Methods

Study subjects

This retrospective cross-sectional study was performed on 136 SLE patients who referred to the Rheumatology Specialist Clinic of Rafsanjan, from the beginning of October 2015 to September 2018. A rheumatologist diagnosed SLE in patients according to the American College of Rheumatology (ACR) criteria for SLE [9]. Data was collected using a checklist; demographic charact-eristics included gender, age, marital status, occupation, educational level, place of residence (urban and rural), smoking, and family history of rheumatic diseases. All patients were examined clinically by a rheumatologist. The history of the disease, medications, and disease activity were recorded for each patient using a checklist. Disease activity was measured using SLEDAI [10]. Dyslipidemia in SLE cases was defined as elevated total cholesterol (> 200 mg/dL), TG (> 200 mg/dL), low-density lipoprotein (LDL; > 100 mg/dL), and decreased HDL (< 40 mg/dL) levels in the serum samples [11].

Blood collection and analysis

After written informed consent was obtained from each study participant, peripheral blood samples were taken after overnight fasting. Serum levels of cholesterol, triglyceride, HDL, and LDL were measured by standard kits and using an autoanalyzer (Hitachi912, Japan).

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) software version 18 was used to analyze the data. For statistical analysis, the normal distribution of quantitative variables was first assessed using the Kolmogorov-Smirnov test. Differences in quantitative variables between the two groups was analyzed using the independent t-test and the Mann-Whitney nonparametric test. Moreover, differences between quantitative variables between several groups were analyzed using the ANOVA test (or Kruskal–Wallis test). Spearman and Pearson's test was used to test the correlation between numerical variables. The significance level in all analyses was considered to be less than 0.05. This study was performed with the permission of the Ethics Council (IR code: IR.RUMS.REC.1397.017).

Results

The baseline, demographic, and clinical data of the 136 SLE patients included in this study are shown in Table 1. In the present study, 119 (87.5%) of the patients were female and 17 (12.5%) of the patients were male. It was observed that 41 (30.2%) subjects were experiencing hypertension, and 62 (45.6%) patients were using lipid-lowering drugs. The SLEDAI of the patients was 13.8±5.9. In this population, 49 patients (36%) had high TG, 56 patients (41.2%) had high cholesterol, 10 patients (7.4%) had high LDL, and 33 patients (24.3%) had low HDL. A family history of rheumatologic diseases was reported in 47.1% of patients, and 66.9% of them reported their occupation as housekeeper (Table 2).

Table 1. Demographic and clinical data among all patients (n = 136).

Variables	Mean ± SD	Min	Max
Age (year)	39.2±10.3	15	61
TG (mg/dl)	139.5±55.6	41	330
Cholesterol (mg/dl)	190.5±31.1	112	272
HDL (mg/dl)	47.3±9.8	27	97
LDL (mg/dl)	113.1±27.7	48	191
SLEDAI	13.8±5.9	2	35

SD; Standard deviation, TG; Triglyceride, HDL; High-density lipoprotein, LDL; Low-density lipoprotein, SLEDAI; Systemic lupus erythematosus disease activity index

Table 2. Study history of diseases and job in rheumatologic diseases

Variables		n	Percentage (%)
History of rheumatologic diseases	Positive	64	47.1
	Negative	72	52.9
	Housekeeper	91	66.9

Variables		n	Percentage (%)
Job	Non-employed	15	11
	Farmer	9	6.6
	Free job	4	2.9
	Others	17	12.5

The TG, cholesterol, and LDL levels were higher in male patients than in female patients, and HDL blood levels were higher in female patients than in males; however, statistical tests did not show any significant difference between the two genders regarding blood lipid levels (Table 3).

Table 3. The mean of lipid profiles in study patients by sex

Variables	Male (n=17)	Female (n=119)	*P value*
TG (mg/dl) [Mean± SD]	141.8±63	139.2±54.7	0.85
Cholesterol (mg/dl)	200.2±27.5	189.2±31.4	0.14
HDL (mg/dl)	47±11.1	47.3±9.6	0.84
LDL (mg / dl)	123.2±23.5	111.6±28	0.07

SD; Standard deviation, TG; Triglyceride, HDL; High-density lipoprotein, LDL; Low-density lipoprotein

In the patients studied, age was positively and significantly correlated with cholesterol (*p value* = 0.009, *r* = 0.224; Figure 1) and LDL levels (*p value* = 0.003 and *r* = 0.256; Figure 2) and negatively and significantly associated with HDL levels (*p value* = 0.023 and *r* = -0.489; Figure 3).
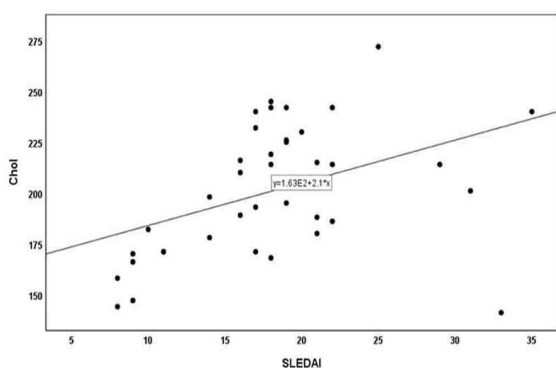

Figure 1. Correlation between cholesterol level and SLEDAI in newly diagnosed patients.
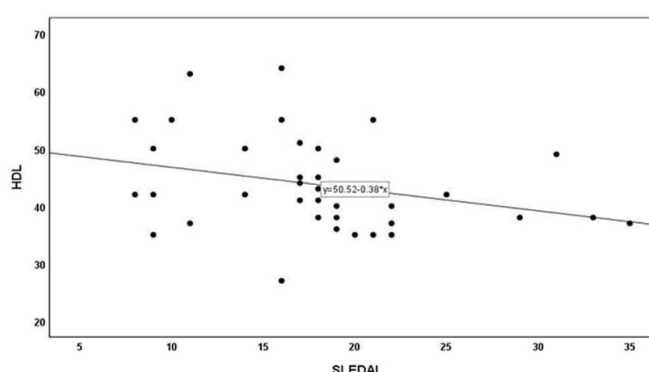

Figure 2. Correlation between HDL level and SLEDAI in newly diagnosed patients.
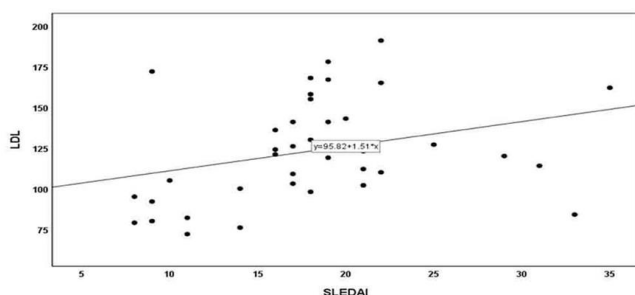

Figure 3. Correlation between

There was no significant correlation between blood TG levels and age (*p value* = 0.274, *r* = 0.074). Blood lipid levels in patients did not show a significant difference (*p value* = 0.147) with education (illiterate, school education, and university education). Blood lipid levels in urban and rural patients were not significantly different (*p value* = 0.611). Moreover, blood lipid levels in smokers and non-smokers were not significantly different (*p value* = 0.389). In newly diagnosed patients, the SLEDAI was positively and significantly correlated with levels of cholesterol (*p*

value = 0.002, r = 0. 489) and LDL (*p value* = 0.009, r = 0.418) and was negatively and significantly correlated with HDL levels (*p value* = 0.037, r = -0.381). No significant correlation was found between serum TG levels and SLEDAI (*p value* = 0.114, r = 0.19). Furthermore, there was no significant difference in SLEDAI scores between subjects using lipid-lowering drugs and those without such treatment (*p value* = 0841).

Discussion

In the current study, the SLE activity index in newly diagnosed lupus patients was positively and significantly associated with cholesterol and LDL and had a negative and significant relationship with HDL, but no significant relationship between triglyceride level and the SLE activity index was observed.

In previous studies, a higher outbreak of dyslipidemia was reported in patients with lupus [12, 13]. Dakua et al. conducted a study in India and reported an outbreak of 57.4% of dyslipidemia in patients with lupus. In their study, mean serum cholesterol, triglyceride, and LDL levels were significantly higher in patients with lupus than the control group, and HDL levels were significantly lower in patients with lupus than the control group [14]. In the study of Abdalla et al., conducted in Egypt, the outbreak of hypert-riglyceridemia and hypercholesterolemia were reported as 33.3% and 47.9%, respectively [15]. Costenbader et al. studied known risk factors for atherosclerosis in 110 patients with lupus and found them in 89% of patients. Moreover, 81% of patients smoked, 80% of patients had hypercholesterolemia, 78% of patients had hypertension, and 50% of patients had diabetes [16]. Petri et al. studied 225 patients with lupus and found diabetes in 27% of them [17]. The higher outbreak of dyslipidemia observed in these patients cannot be justified by the level of education of patients, as no significant differences were observed in the levels of blood lipids in patients with different educational levels (illiterate, school education, and university education).

Various mechanisms can explain the relationship between lupus and dyslipidemia. Lupus is a chronic inflammatory disease, and the potential role of inflammation in the regulation of the lipoprotein lipase (LPL) enzyme has recently been considered [18] following the identification of the effects of TNF-α, IL-1, and IFN-γ on the significant reduction of enzyme activity of LPL. Moreover, acute phase responders change the hepatocyte synthesis of a broad chain of proteins involved in the metabolism of lipoproteins, coagulation, and the complement system [19]. Therefore, it seems that their inflammatory conditions alone can cause specific changes in lipid profiles. Increased production of these cytokines, including IL-6, is a characteristic of lupus, especially during the period of increased disease activity and plays a role in the dyslipoproteinaemia associated with lupus [20]. Recently, it has been shown that the circulating levels of TNF-α in lupus patients have increased, and this increase is associated with the activity of the disease and triglyceride levels [21]. Lupus and other autoimmune diseases also

create a large number of autoantibodies that cause the formation of pseudo-enzyme like lipoprotein lipase (anti-LPL) or disrupt the apolipoprotein catabolism and create various types of dyslipidemia [22, 23] and may cause autoimmune hyperlipidemia [24].

While most studies confirm the association between lupus and its severity with dyslipidemia, Sabio et al. reported slightly higher triglyceride levels in lupus patients with metabolic syndrome than in the control group with metabolic syndrome, and cholesterol and LDL were significantly lower than the control group in lupus patients with metabolic syndrome. It should be noted that patients with lupus present in the study of Sabio et al. were all diagnosed more than one year earlier, and treatment was initiated then [25].

Drugs used in the treatment of lupus can also affect lipid profiles. Chronic steroid use in lupus patients can increase LDL, HDL, and triglyceride levels [26, 27]. Steroids have a great influence on lipid metabolism, including increased insulin resistance, increased LPL activity, increased lipolysis, and inhibition of free fatty acid β-oxidation [28]. Undoubtedly, the effect of steroids is based on dose-dependent effects, so that dosages of less than 10 mg do not have a significant effect on lipid profiles [29]. Cyclosporine A also affects lipid metabolism. In a previous study, this drug caused dyslipidemia in 5% of patients [30]. In the futurist study of hydroxychloroquine, which is used long-term in the treatment of lupus, its favorable effects on profile lipids were observed [31]. The current study evaluated the blood lipids levels of newly diagnosed lupus patients, and thus, the treatment of lupus that could affect lipid profiles of patients was not started for these patients. This point is one of the strengths of the current study.

Blood levels of TG, cholesterol, LDL, and HDL were not significantly different in between male and female participants of the current study. In the patients studied, age was positively and significantly associated with cholesterol and LDL and negatively and significantly associated with HDL. There was no significant relationship between blood triglyceride levels and age. In general, lupus is a disease that often affects people between the ages of 20-30. Another point to be taken into account is that in older lupus patients, other concomitant factors may predominate over lupus-associated factors and cause dyslipidemia in these patients [32].

In this study, the levels of blood lipids in patients with different educational levels (illiterate, school education, and university education) were not significantly different. A 2006 study by Albert et al. found that in non-lupus women, education was a protective factor against dyslipidemia [33].

The strengths of the current study were the inclusion of a high number of newly diagnosed lupus patients and the investigation of the relationship between severity of disease and lipid profiles in patients. On the other hand, one of the limitations of the present study is the absence of the possibility of recording the levels of other lipid

metabolism biomarkers and inflammatory markers to determine their association with lipid profiles. Other limitations were the study design (cross-sectional), presence of potential confounding variables, and relatively small sample size.

Conclusion

Based on the results of this study, the SLE activity index in newly diagnosed lupus patients was positively and significantly related to cholesterol and LDL and was negatively and significantly related to HDL; however, no significant correlation was found between blood triglyceride levels and the SLE activity index. Therefore, these patients should be screened for profile lipid disorders at the time of diagnosis as well as the course of treatment. As some patients may use steroids for symptom control, this confounding factor should have been evaluated in our study. Moreover, other conditions that might affect lipid profile concentrations, including Hashimoto thyroiditis was not evaluated in this survey. Therefore, more studies are essential to evaluate the relationship between the

severity of lupus disease and the levels of lipid metabolism biomarkers with consideration given the confounding factor mentioned above.

Authors' contributions

MR contributed to the conception and design of the work.

AA contributed to the acquisition, analysis, and interpretation of data.

MA contributed to the drafting, revising, and final approval of the manuscript.

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Conflict of interest statement
None.

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