The Relationship Between Dyslipidemia and Lupus Nephritis in Systemic Lupus Erythematosus Patients Attending a Saudi Rheumatic Center, Tabuk

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Abstract

Background: There is an increasing awareness of the role of dyslipidemia in lupus nephritis patients, no researchers have studied dyslipidemia in systemic lupus erythematosus (SLE) in Tabuk. In this study, we aimed to investigate the association between dyslipidemia and lupus nephritis in Tabuk, Saudi Arabia.

Methods: This cross-sectional comparative longitudinal hospital-based study was conducted at a rheumatic clinic in the North West Armed Force Hospital (NWAFH) during the period April 2014–June 2015. Seventy-three patients diagnosed with SLE were invited to participate in the study. All participants were required to sign a written informed consent, following which they were interviewed using a structured questionnaire. Data collected include demographic data, clinical characteristics, fasting lipid profile, renal function tests, urine analysis, antinuclear antibody, anti-double-stranded antibodies, complement levels, serum albumin, anticardiolipin antibodies, and antiphospholipid antibodies. Lupus nephritis was ascertained by renal biopsy. The research was approved by the ethical committees of both the University of Tabuk and the NWAFH and data were analyzed using the Statistical Package for Social Sciences (SPSS).

Results: Out of 73 patients with SLE, 86.3% were females with a mean age of 34 ± 6.4 years. Lupus nephritis was evident in 26% of the patients, proteinuria in 44.1%, high total cholesterol in 17.8%, high low-density lipoprotein in 15.1%, high triglycerides in 27.3%, and low high-density lipoproteins in 52.1%. Patients with lupus nephritis had high total cholesterol, high LDL, high TG, and low HDL than those without lupus nephritis p < 0.05.

Conclusion: Dyslipidemia was more common among patients with SLE nephritis, and an aggressive treatment is recommended to reduce this serious complication. The relatively small size of the study group and the fact that the study was conducted at a single tertiary center are the limitations of this study.

Key words: Dyslipidemia, lupus nephritis, Saudi Arabia
Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease found in women in their childbearing age; nearly one-fifth of the cases occur in the first two decades of a woman’s life. The disease runs a remitting-relapsing course with breakout difficult to control. Cardiovascular disease is the most common cause of death among patients that acquire the disease for more than five years [1].

Accelerated atherosclerosis and premature ischemic heart disease are common causes of mortality and morbidity among patients with SLE. Increasing age is a risk factor for coronary heart disease but unlike the general population, young women with SLE are more affected. The potential for cardiovascular disease including myocardial infarction, cerebrovascular and peripheral arterial disease in young women with SLE is approximately double than that in the general population [2, 3].

Several pathophysiological mechanisms mediate coronary heart disease including atherosclerosis, arteritis, thrombosis, spasm, embolization, and abnormal coronary flow [4]. It is strongly suggested by epidemiological studies that in addition to conventional coronary risk factors, there are non-classical risks in SLE patients, in fact, SLE is considered an independent risk factor for atherosclerosis [5, 6].

A recently published research concluded that regardless of food intake and nutritional status, preserved kidney function, low disease activity, and low steroid dose, adolescent females with SLE have proatherogenic lipid biomarkers that may contribute to atherosclerosis risks [7].

In this regard, dyslipidemia was found to be prevalent in SLE patients (55–77%), especially among those with active disease, heavy proteinuria, and concomitant medications. Furthermore, cardiovascular complications are the leading cause of death among SLE patients with renal failure, and renal impairment was found to be associated with dyslipidemia [8].

No researcher has studied dyslipidemia in SLE patients in Tabuk, Saudi Arabia. Thus, the present study was conducted to investigate the relationship of dyslipidemia among patients with SLE in Tabuk.

Materials and Methods

This cross-sectional descriptive, longitudinal, hospital-based study was conducted between June 2014 and April 2015 among patients attending the rheumatic outpatients’
Seventy-three patients above the age of 18 years diagnosed with SLE based on the American College of Rheumatology Criteria (ACR) [9] signed a written informed consent form before being interviewed and examined by the researcher (a rheumatologist). A structured questionnaire was used to obtain sociodemographic data and clinical characteristics including lupus nephritis based on renal biopsy findings, myocardial infarction, stroke, infections, hypertension, pre-hypertension, and hypotension. All patients were in remission at the time of lipid measurements as indicated by serological markers. Patients with active disease were excluded from the study as well as those on steroid dose >10 mg/day, diabetic patients, patients with nephrotic range proteinuria, those with chronic liver disease or active malignancy, patients diagnosed with familial dyslipidemias, active thyroid disorders, and patients on oral contraceptive pills. The following investigations were undertaken: urinalysis for RBCs cast, albumin, and pus cells, full blood count, complement level, erythrocyte sedimentation rate (ESR), high sensitive C-reactive protein (CRP), and antinuclear antibody profile (ANA).

Total cholesterol and triglycerides were measured using a colorimetric enzyme assay (NingBo RuiYuan Biotechnology Co., Ltd., Zhejiang, China). HDL-C and LDL-C were quantified using the GPO–PAP method (Beckman Coulter, Miami, FL, USA). The urease method from BUN Healthcare Diagnostics Newark DE 19714 USA was used for blood urea nitrogen measurement, and serum creatinine was ascertained using CREA Healthcare Diagnostics Newark, DE 19714 USA based on the idea that in the presence of NaOH, pectate reacts with creatinine to form a red chromophore measurable by bichromatic (510e600).

For the purpose of this research, the following definitions were adopted:

- Hypertension: self-reported, on antihypertensive therapy, history of systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg.
- Abnormal lipid profile: total cholesterol [TC] ≥5.18 mmol/L; triglyceride [TG] ≥2.26 mmol/L; high-density lipoprotein cholesterol [HDL-C] <0.91 mmol/L; low-density lipoprotein cholesterol [LDL-C] ≥3.37 mmol/L, according to the Adult Treatment Panel III criteria [10].

The ethical committee of the University of Tabuk and the local committee approved the research, and the Statistical Package for Social Sciences was used for data analysis. The Chi-square test was used to compare categorical data, and data were presented as a mean ± SD and percentages unless otherwise specified with a p < 0.05 considered as significant.
Results

Female dominance (86.3%) was obvious in the 73 studied patients, their age ranged from 20 to 50 years with a mean age of 34 ± 6.4 years. Lupus nephritis was found in 26% of the patients, stroke was evident in 8.2%, while myocardial infarction was concluded in 1.4% of the SLE patients. Other clinical characteristics are shown in Table 1. Table 2 illustrates the laboratory investigations among SLE patients in which high total cholesterol was found in 17.8%, high LDL in 15.1%, high triglycerides in 27.3%, while low HDL was observed in 52.1%. In the present study, proteinuria was found in 44.1% of the SLE patients, RBCS cast was found in 27.5%, raised urea and creatinine were observed in 7.9%, and low serum albumin in 71.45. Regarding immunological screening, ANA was positive in 98.6%, antidualle stranded antibody was positive in 100%, antismith antibodies were positive in 26%, anticardiolipin was positive in 13.7%, antiphospholipid was positive in 3.9%, while antiribonucleoprotein was positive in 20.5%.

**Table 1: Clinical Characteristics of Systemic Lupus Erythematosus Patients.**

| Character                          | No. (%) |
|-----------------------------------|---------|
| Lupus nephritis                   | 19 (26%)|
| Stroke                            | 6 (8.2%)|
| Myocardial infarction             | 1 (1.4%)|
| Pulmonary embolism                | 4 (5.5%)|
| Neuropsychiatric manifestations   | 26 (35.6%)|
| Hypertension                      | 11 (15.1%)|
| Prehypertension                   | 19 (26%)|
| Hypotension                       | 25 (34.2%)|
| Infections                        | 10 (13.7%)|

**Table 2: Laboratory Investigations of SLE Patients.**

| Investigation                        | No. (%) |
|--------------------------------------|---------|
| High total cholesterol               | 13 (17.8%)|
| High LDL                             | 11 (15.1%)|
| High TG                              | 20 (27.3%)|
| Low HDL                              | 38 (52.1%)|
| Proteinuria                          | 30 (44.1%)|
| Red blood cells cast                 | 19 (27.5%)|
| Raised urea & creatinine             | 5 (7.9%)|
| Low albumin                          | 45 (71.4%)|
| Antinuclear antibodies positive      | 72 (98.6%)|
| Antidoubles stranded antibodies      | 73 (100%)|
| Antismith antibodies positive        | 19 (26%)|
| Anticardiolipin positive             | 10 (13.7%)|
| Antiphospholipid positive            | 3 (3.9%)|
| Antiribonucleoprotein positive       | 15 (20.5%)|
In the current study, the total cholesterol was higher among patients with SLE nephropathy 5.40 ± 1.46 mmol/l vs 4.36 ± 0.82 with a significant statistical difference, \( p \) value was 0.003, LDL was 3.13 ± 0.82 mmol/l vs 2.66 ± 0.53 in patients with nephropathy and those without nephropathy, respectively, with significant statistical difference, \( p = 0.028 \); triglycerides were higher in lupus nephritis 2.31 ± 1.54 mmol/l vs 1.28 ± 0.72 with a \( p = 0.003 \), no significant statistical difference was evident regarding high-density lipoproteins levels (see Table 3).

| TABLE 3: The Relationship Between Dyslipidemia and Lupus Nephritis. |
|---------------------------------------------------------------|
|                      Lupus nephritis | Others  | \( p \) value |
|------------------------|----------|--------------|
| **Total cholesterol**  |          |              |
| (>5.2 mmol)            | 5.40 ± 1.46 | 4.36 ± 0.82  | 0.0036      |
| **Triglycerides**      |          |              |
| (>1.7 mmol)            | 2.31 ± 1.54 | 1.28 ± 0.72  | 0.0033      |
| **LDL**                |          |              |
| (>3.4)                 | 3.13 ± 0.82 | 2.66 ± 0.53  | 0.0285      |
| **HDL**                |          |              |
| (Male <1 mmol; Female <1.5 mmol) | 1.11 ± 0.32 | 1.18 ± 0.23  | 0.3901      |

In the current data, the total cholesterol was higher among patients with proteinuria 5.20 ± 1.31 mmol/liter vs 4.28 ± 0.88 with a significant statistical difference of \( p \) value 0.007, LDL was higher among patients with proteinuria 3.06 ± 0.73 vs 2.60 ± 0.52 with a significant statistical difference of \( p \) value 0.024. Table 4 depicts the relationship between lipid profile and proteinuria among SLE patients.

| TABLE 4: The Relationship of Dyslipidemia and Proteinuria. |
|----------------------------------------------------------|
|                        Proteinuria | Others  | \( p \) value |
|---------------------------|----------|--------------|
| **Total cholesterol**     |          |              |
| (>5.2 mmol)               | 5.20 ± 1.31 | 4.28 ± 0.88  | 0.0076      |
| **Triglycerides**         |          |              |
| (>1.7 mmol)               | 2.03 ± 1.43 | 1.26 ± 0.76  | 0.0271      |
| **LDL**                   |          |              |
| (>3.4)                    | 3.06 ± 0.73 | 2.60 ± 0.56  | 0.0248      |
| **HDL**                   |          |              |
| (Male <1 mmol; Female <1.5 mmol) | 1.12 ± 0.29 | 1.20 ± 0.24  | 0.2736      |

The triglycerides levels were higher among patients with neuropsychiatric manifestations compared to those without 1.96 ± 1.4 mmol/l vs 1.43 ± 0.92 with a significant statistical difference of \( p = 0.019 \); total cholesterol was higher among neuropsychiatric patients 4.88 ± 1.4 vs 4.63 ± 1.02 with no significant statistical difference of \( p = 0.512 \). Table 5 shows the relationship between lipid profile and neuropsychiatric manifestations.
T/A.smcp/B.smcp/L.smcp/E.smcp 5: The Relationship Between Neuropsychiatric Manifestations and Dyslipidemia.

|                         | Neuropsychiatry | Others  | \( p \) value |
|-------------------------|-----------------|---------|---------------|
| **Total cholesterol**   |                 |         |               |
| (>5.2 mmol)             | 4.88 ± 1.4      | 4.63 ± 1.02 | 0.5121        |
| **Triglycerides**       |                 |         |               |
| (>1.7 mmol)             | 1.96 ± 1.4      | 1.43 ± 0.92 | 0.0195        |
| **LDL**                 |                 |         |               |
| (>3.4)                  | 2.98 ± 0.74     | 2.74 ± 0.63 | 0.2713        |
| **HDL**                 |                 |         |               |
| (Male <1 mmol; Female <1.5 mmol) | 1.206 ± 0.27    | 1.07 ± 0.23 | 0.0995        |

The total cholesterol level was 4.65 ± 0.70 mmol/l in patients with low complement level, and 4.71 ± 1.26 in patients with normal complements with no significant statistical difference of \( p = 0.885 \); triglycerides were 1.46 ± 1.09 in patients with low complement level vs 1.65 ± 1.17 in patients with normal complement level with no significant statistical difference of \( p = 0.652 \). Table 6 illustrates the relationship between the complement level and lipid profile.

T/A.smcp/B.smcp/L.smcp/E.smcp 6: The Relationship Between Dyslipidemia and Complements Level.

|                         | Complement Cascade (Normal) | Complement Cascade (Low) | \( p \) value |
|-------------------------|-----------------------------|--------------------------|---------------|
| **Total cholesterol**   |                             |                          |               |
| (>5.2 mmol)             | 4.71 ± 1.26                 | 4.65 ± 0.70              | 0.8851        |
| **Triglycerides**       |                             |                          |               |
| (>1.7 mmol)             | 1.65 ± 1.17                 | 1.46 ± 1.09              | 0.6520        |
| **LDL**                 |                             |                          |               |
| (>3.4)                  | 2.85 ± 0.69                 | 2.70 ± 0.59              | 0.5677        |
| **HDL**                 |                             |                          |               |
| (Male <1 mmol; Female <1.5 mmol) | 1.25 ± 0.26                | 1.29 ± 0.24              | 0.0873        |

The relationship between the serum albumin and lipid profile are shown in Table 7 in which the total cholesterol was 4.86 ± 1.38 mmol/l in patients with low serum albumin vs 4.48 ± 0.46 mmol/l in patients with normal serum albumin with no statistically significant difference of \( p = 0.337 \); TG was 1.26 ± 0.59 mmol/l vs 1.87 ± 1.30 in patients with low and normal serum albumin, respectively, with \( p = 0.114 \); LDL was 2.91 ± 0.71 mmol/l among patients with low albumin vs 2.78 ± 0.48 in normal serum albumin patients with \( p = 0.583 \); while HDL level was 1.14 ± 0.27 mmol/l and 1.14 ± 0.23 among patients with low and normal serum albumin, respectively, with \( p = 0.933 \).
### TABLE 7: The Relationship Between Dyslipidemia and Serum Albumin.

|                         | Albumin (<35) | Albumin (>35) | p value |
|-------------------------|---------------|---------------|---------|
| Total cholesterol       |               |               |         |
| (>5.2 mmol)             | 4.86 + 1.38   | 4.48 + 0.46   | 0.3375  |
| Triglycerides           |               |               |         |
| (>1.7 mmol)             | 1.26 + 0.59   | 1.87 + 1.30   | 0.1141  |
| LDL                     |               |               |         |
| (>3.4)                  | 2.91 + 0.71   | 2.78 + 0.48   | 0.5835  |
| HDL                     |               |               |         |
| (Male <1 mmol; Female <1.5 mmol) | 1.14 + 0.27   | 1.14 + 0.23   | 0.9339  |

### Discussion

Advances in immunosuppressive therapy and supportive care have improved the survival and short-term clinical outcomes of SLE patients, with a substantial improvement in the cardiovascular morbidity and mortality, there is an increasing awareness of dyslipidemia as a major vascular risk among these patients [11].

The present data showed high total cholesterol in 17.8%, high LDL in 15.1%, high triglycerides in 27.3%, and low HDL in 52.1% of SLE patients, hypercholesterolemia was higher than in an epidemiological study conducted among Saudi patients [12] and hypercholesterolemia was found in 8.5%. A study published in Jakarta found high total cholesterol, high LDL, high triglycerides, and low HDL in 43%, 26.4%, 44.2%, and 26% of SLE patients, respectively [13]. The difference in the percentages of the lipid profile can be attributed to genetic and dietary factors and the level of exercise in the two studies.

Formiga et al. [14] reported that 55% of young premenopausal SLE women with preserved renal function had dyslipoproteinemia, similar to the current study in which 52.1% of SLE patients had dyslipidemia; another observational study conducted among children with SLE [15] reported dyslipidemia in 63% of the subjects in accordance with the current data.

In the present study, patients with lupus nephritis had higher total cholesterol, triglycerides, low-density lipoprotein, and lower high-density lipoprotein than those without lupus nephritis similar to Chong et al.’s [8] who reported higher cholesterol and triglycerides and lower HDL in lupus nephritis patients compared to control subjects.

In the current research, a positive correlation was evident between dyslipidemias (high total cholesterol, high TG, high LDL, and low HDL) and proteinuria similar to Formiga et al.’s [14] and Kashef et al.’s [16] studies, who found a positive correlation between dyslipidemias and proteinuria. Chong et al. [8] reported no correlation between...
proteinuria and dyslipidemia in contradiction to the present findings, a plausible explanation is the lower level of proteinuria in Chong et al.’s study.

In the current study the total serum cholesterol in SLE patients with lupus nephropathy was 5.4 ± 1.4 mmol/l and was positively correlated with proteinuria and lupus nephritis; similarly, Tisseverasinghe et al. found that the serum cholesterol exceeds 5.2 mmol/l in SLE patients and was associated with mortality and adverse renal outcomes [17].

Previous literature concluded that hyperlipidemia will enhance renal immune complex-mediated complement activation and development of nephritis, in the current study, hyperlipidemia was positively correlated with proteinuria and lupus nephritis confirming the aforementioned observation [18]. In the present study, a correlation was found between hypocomplementemia and dyslipidemia that can be explained by the small size of our study.

In the present study, low-density lipoprotein was high in 14.8% and was in positive correlation with proteinuria and SLE nephropathy, in accordance with Olusi and George who concluded a prevalence of atherogenic LDL in 52% of SLE patients [19].

**Limitations:** The study limitation was the small size of the study group, also we could not control for the therapy taken for SLE treatment like hydroxychloroquine which can decrease the lipids through various mechanisms.

**Conclusion**

Dyslipidemia was found to be higher among patients with SLE compared to the Saudi general population and was positively correlated with SLE nephropathy and proteinuria. Aggressive treatment of dyslipidemia could decrease nephropathy and overall cardiovascular risk.

**Conflict of Interest**

The authors declare no conflict of interest.

**Disclaimer:** The views expressed in the submitted article are author’s own and not an official position of the institution or funder.

**Authors Contribution**

- Concept and design: Dr. Hyder Mirghani
- Data collection: Dr. Hyder Mirghani, Dr. Osama Salih
- Data analysis: Dr. Hyder Mirghani
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- All authors approved the final version for publication and are accountable for the accuracy and integrity of all aspects of the work.

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