Clinical Rheumatology (2018) 37:1539–1546
https://doi.org/10.1007/s10067-018-4051-0

ORIGINAL ARTICLE

Clinical and laboratory aspects of dyslipidemia in Brazilian women with systemic lupus erythematosus

Ajax M. Atta[1] · João Paulo C. G. Silva[2] · Mittermayer B. Santiago[3] · Isabela S. Oliveira[1] · Rodrigo C. Oliveira[1] · Maria Luiza B. Sousa Atta[1]

Received: 20 September 2017 / Revised: 3 January 2018 / Accepted: 22 February 2018 / Published online: 8 March 2018

Abstract

Systemic lupus erythematosus (SLE) is associated with dyslipidemia, atherosclerosis, and cardiovascular disease. In this study, we investigated the presence of dyslipidemia in Brazilian SLE patients by evaluating their lipid profile and immune status, including the production of autoantibodies and cytokines involved in atherogenesis. Ninety-four female SLE patients participated in this study and, based on their lipid profile, were classified as dyslipidemic or not. All were tested for antinuclear antibodies (ANAs), antiphospholipid antibodies, and autoantibodies to extractable nuclear antigens and double-stranded DNA. Serum levels of apolipoproteins A and B, C3, C4, and C-reactive protein were measured, as well as serum levels of interleukin (IL)-6, tumor necrosis factor (TNF)-α, and IL-10. Lupus activity was scored according to the Systemic Lupus Erythematosus Disease Activity Index 2000. Sixty-nine patients (73.4%) had dyslipidemia, and the remaining 25 patients (26.6%) were non-dyslipidemic. Lupus activity was correlated with non-high-density lipoprotein cholesterol and triglyceride (TG) levels (non-HDL-C, $r = 0.34$ and $p = 0.0043$ and $r = 0.46$ and $p < 0.0001$, respectively). Atherogenic indexes apolipoprotein B/apolipoprotein A and TG:HDL-C ratios were higher in dyslipidemic women, and TG:HDL was correlated with disease activity ($r = 0.40$, $p = 0.0007$). IL-6, TNF-α, and IL-10 levels were similar between groups; however, a positive correlation between IL-6 and CRP levels was only observed in the group with dyslipidemia ($r = 0.55$, $p < 0.0001$). Female Brazilian SLE patients present a high prevalence of dyslipidemia and exhibit a higher risk of cardiovascular diseases as compared with female SLE patients without dyslipidemia and healthy individuals.

Keywords Autoantibody · Cytokine · Dyslipidemia · Systemic lupus erythematosus

Introduction

An important clinical manifestation of systemic lupus erythematosus (SLE) is dyslipidemia and, consequently, associated atherosclerosis and cardiovascular diseases (CVDs). Currently, the estimated prevalence of subclinical atherosclerosis in lupus patients is high according to examination of the carotid artery by ultrasonography, tomography, magnetic resonance imaging, and perfusion studies. Evidence also suggests that cardiovascular events and cerebral disease affect between 6 and 22% of patients with SLE [1, 2]. However, the differences in prevalence among studies are associated with variations in lupus activity and the methodologies employed in their determination [3]. The Framingham study verified that women aged 35 to 44 years with lupus have a 50-fold greater risk of myocardial infarction as compared with women of the same age in the general population without SLE, with such cardiovascular events occurring more frequently in premenopausal women [4, 5]. The risk factors for CVD in lupus patients are similar to those already known in the general population (obesity, hypertension, and insulin resistance, among others). However, the Toronto Risk Factor Study demonstrated a greater number of risk factors in SLE patients relative to those usually observed in people without lupus. However, the prevention of future cardiovascular events in these individuals does not appear to be avoided

✉ Ajax M. Atta
ajaxmatta@gmail.com

[1] Laboratório de Pesquisa em Imunologia, Faculdade de Farmácia, Universidade Federal da Bahia, Salvador, Bahia 40170115, Brazil

[2] Programa de Pós-Graduação em Imunologia, Universidade Federal da Bahia, Salvador, Brazil

[3] Escola Bahiana de Medicina e Saúde Pública, Salvador, Brazil

efficiently through clinical and therapeutic interventions [6–8]. Other factors, including corticoid therapy and the presence of antiphospholipid antibodies (aPLs), especially anti-β2 glycoprotein I (β2GPI), anticardiolipin antibodies, antiphosphatidylserine, and anti-Annexin V, could facilitate the occurrence of atherosclerosis in SLE patients. However, the role of these antibodies in the pathogenesis of CDVs is still under investigation [1, 9, 10]. The presence of a systemic inflammatory reaction and increased levels of certain atherogenic cytokines, such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α, as well as antibodies associated with atherogenesis, stimulate the interest of researchers and justify the need for additional studies to identify associations between SLE-specific immune dysregulation and the development of atherogenesis in different geographical populations. This study investigated the presence of dyslipidemia, atherogenic cytokines, and laboratory biomarkers indicating the risk of CVDs in patients with SLE residing in Salvador, Bahia (Brazil).

Patients and methods

Patients

This study included a group of female patients with a diagnosis of SLE based on the criteria from the American College of Rheumatology (ACR) [11] and consecutively treated in the outpatient clinic for lupus of the Bahia School of Medicine and Public Health. SLE activity was measured according to Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) [12]. Pregnant women and patients with viral infections (human immunodeficiency virus, hepatitis B virus, and hepatitis C virus) were not included in the study, which was approved by the Ethics Committee of the Bahia School of Medicine and Public Health. Dyslipidemia was diagnosed in accordance with the V Brazilian Guidelines on Dyslipidemia and the Prevention of Atherosclerosis [13]. Four types of dyslipidemia were investigated: isolated hypercholesterolemia [low-density lipoprotein cholesterol (LDL-C) ≥ 160 mg/dL], isolated hypertriglyceridemia [triglyceride (TG) ≥ 150 mg/dL), mixed hyperlipidemia (LDL-C ≥ 160 mg/dL and TG ≥ 150 mg/dL), and low high-density lipoprotein cholesterol (HDL-C) (< 50 mg/dL), isolated or associated with increased LDL-C or TG. The serum level of non-HDL was calculated from total cholesterol by subtracting the level of HDL-C (normal < 160 mg/dL). Most patients made use of chloroquine (71/94; 75.5%), followed by, in descending order of use, prednisone (62/94; 66%; mean dose = 15 mg/day), azathioprine (50/94; 53.2%), methotrexate (24/94; 25.5%), or, less often, cyclosporine (7/94; 7.4%).

Autoantibodies

Antinuclear autoantibodies (ANAs) were identified by an indirect fluorescent-antibody test using an antigenic substrate of HEp-2 cells diluted 1:40 in serum and an anti-human IgG conjugate labeled with fluorescein isothiocyanate (Viro-Immun; Labor-Diagnostika GmbH, Düsseldorf, Germany). Antibodies to double-stranded DNA (dsDNA), Sm, SS-A/Ro, SS-B/La, Sm/ribonucleoprotein (RNP), nucleosome, ribosomal protein P (Rib-P), as well as phospholipid antibodies, were tested by indirect enzyme-linked immunosorbent assay (ELISA; Orgentec Diagnostika, Mainz, Germany).

Determination of serum cytokine levels

Serum levels of IL-6, TNF-α, and IL-10 were determined by capture ELISA (eBioscience, San Diego, CA, USA and Bender MedSystems, Vienna, Austria). The sensitivity limits of the immunoassays were 2.0 pg/mL for IL-6 and IL-10 and 4.0 pg/mL for TNF-α.

Determination of serum C3, C4, and C-reactive protein levels

Serum levels of apolipoprotein A (apoA) and apolipoprotein B (apoB) (normal ranges 105–205 and 55–130 mg/dL, respectively), complement C3 and C4 (normal ranges 67–149 and 10–38 mg/dL, respectively), and C-reactive protein (CRP) were determined by nephelometry (IMMAGE; Beckman-Coulter, Brea, CA, USA). CRP was measured with an ultrasensitive immunoassay with an analytical sensitivity of 0.06 mg/L. CRP levels > 3.0 mg/L were suggestive of CVD risk.

Biochemical analyses

Serum glucose, total cholesterol, and TG levels were measured in 8 h fasting blood samples of the patients by enzymatic techniques in the biochemical laboratory at the Pharmacy Faculty (Federal Bahia University) using the LABMAX 240 analyzer (Lab Test Diagnostics SA, Lagoa Santa, Minas Gerais, Brazil). HDL-C was determined by direct testing (HDL, LE; Lab Test Diagnostics SA). LDL levels were calculated according to Friedwald's formula [14]. Atherogenic indexes included apoB:apoA ratio (CVD risk ≥ 0.8) and triglyceride:HDL-C ratio (CVD risk ≥ 4.0).

Statistical analysis

The distribution of continuous variables was analyzed by D'Agostino and Pearson tests, and results were expressed as mean ± standard deviation (SD) or median and interquartile range (IQR; Q1–Q3) according to the distribution. The

difference between the medians of two groups was determined by the Mann–Whitney *U* test, and their means were compared using Student's *t* test. Three groups were compared using the Kruskal–Wallis test and Dunn's post hoc test. All variables with a normal distribution after logarithmic transformation were tested by parametric tests. Correlation analyses were performed using the Spearman rank test. Prism 6.0 software (GraphPad, San Diego, CA, USA) was used for the analysis of descriptive statistics. A $p < 0.05$ indicated a statistically significant difference.

Results

Demographic, clinical, and laboratory characteristics

Ninety-four patients were included in the study, and the mean age at the time of evaluation was 40.2 ± 11.9 years. The median duration of disease was 8 years, ranging from 5 to 13 years. All patients had a SLEDAI-2K score ≥ 4. The main clinical manifestations were (in descending order of prevalence) arthritis, photosensitivity, malar rash, and renal dysfunction. Some patients had a clinical report of cardiovascular events. For example, eight patients had a history of stroke, and acute myocardial infarction (AMI) was reported in two patients (Table 1).

Table 1 Demographic and clinical findings in 94 women with SLE

Age (years)	40.2 ± 11.9
SLEDAI-2K	6 (4–10)
Disease duration (years)	8 (5–13)
Arthritis (%)	92/94 (97.9%)
Photosensitivity (%)	72/94 (76.6%)
Malar rash (%)	60/94 (63.85%)
Renal dysfunction (%)	46/94 (48.9%)

Results are expressed as the mean ± SD, median, and IQR or proportion (%)

Characterization of the patient groups by type of dyslipidemia

The presence and type of dyslipidemia in a lupus patient were identified using the criteria of the V Brazilian Guidelines on Dyslipidemias and Prevention of Atherosclerosis [13]. Evaluation of the 94 patients revealed that 69 (73.4%) exhibited some form of dyslipidemia, comprising the lupus group with this lipid disorder. The remaining 25 patients (26.6%) formed the control group of non-dyslipidemic subjects. Among the patients with dyslipidemia, 2/69 (2.9%) exhibited isolated hypertriglyceridemia (TG ≥ 150 mg/dL), 4/69 (5.8%) isolated hypercholesterolemia (LDL-C ≥ 160 mg/dL), 13/69 (18.8%) mixed hyperlipidemia with increased values of LDL-C (≥160 mg/dL) and TG (≥150 mg/dl), and 50/69 (72.5%) low HDL-C (≤ 50 mg/dL) alone or in association with an increase in LDL-C and TG levels.

Lipid profiles

The levels of total cholesterol and ApoB were similar in both groups. However, differences were observed in the levels of non-HDL cholesterol, apoA, and TG, which were higher in the group with dyslipidemia (Table 2). The atherogenic indexes apoB:apoA and TG:HDL-C ratios were also different between groups, with higher ratios observed in SLE patients with dyslipidemia (Fig. 1). The upper limit for these indexes was validated for women from the local population without dyslipidemia. In the group with dyslipidemia, there was a positive correlation between lupus activity and both non-HDL-C and TG levels and the TG:HDL-C ratio (Fig. 2).

Immunological findings

ANAs were detected in SLE patients with and without dyslipidemia. Although antibodies to isolated cell antigens (nucleosome, Sm, SS-A/Ro, SS-B/La, RNP, and Rib-P) were found in both groups, only phospholipid antibodies of the IgA isotype (anti-β2GPI IgA antibodies) were detected in the group without dyslipidemia, but with low prevalence. There was no difference in serum C3 and C4 levels between these patient groups (Table 3).

Although CRP levels were similar in both groups (non-dyslipidemic CRP = 0.457 mg/L, IQR = 0.201–0.922 mg/L; dyslipidemic CRP = 0.492 mg/L, IQR = 0.238–0.926 mg/L), there was a positive correlation between IL-6 and CRP levels in the group of patients with dyslipidemia (Fig. 3). Additionally, serum IL-6, IL-10, and TNF-α levels were similar in lupus patients, regardless of dyslipidemia profile (Table 4).

Discussion

In this study, we investigated the presence of dyslipidemia in women with SLE treated as a referral service for rheumatology in the city of Salvador (Bahia, Brazil) and the possible CVD risk factors associated with this metabolic disorder. This study included only women due to the low prevalence of SLE in male patients in Brazil, as documented in previous studies [15–17]. Our findings of the prevalence and the distribution of SLE-patient lipid profiles agreed with those reported previously [15–17]. Most patients (95%) were aged between 38 and 43 years, of African descent and had four or more criteria recommended by the ACR for SLE [11]. There was a high prevalence of dyslipidemia in this group of SLE patients, including the four types of dyslipidemias established by

Table 2 Lipid profile in SLE women with or without dyslipidemia

Lipid (mg/dL)	Without dyslipidemia ($n = 25$)	Dyslipidemia ($n = 69$)	p
Total cholesterol	189 ± 30	204 ± 76	> 0.05
TG	106 (75–115)	134 (95–205)	< 0.0001
Non-HDL-C	131 ± 29	162 ± 67	0.0270
ApoA	240 ± 30	203 ± 56	< 0.0001
ApoB	92 ± 41	76 ± 21	> 0.05
ApoB:ApoA	0.33 (0.28–0.40)	0.43 (0.33–0.54)	0.0005
TG:HDL-C	1.8 (1.3–2.0)	3.3 (2.5–4.6)	< 0.0001

The results are expressed as the mean ± SD or median with IQR (25–75%). The V Brazilian Guidelines on Dyslipidemias and Prevention of Atherosclerosis (2013) was used to classify the patients. Groups were compared using Student's t test, and the Mann–Whitney U test was used to compare the medians

the V Brazilian Guidelines for Dyslipidemia and Prevention of Atherosclerosis [13], with a predominance of the pattern represented by low HDL-C levels alone or associated with increased LDL-C or TG levels. This finding confirmed earlier results obtained in population studies conducted in Brazil and other countries [15–19]. Risk factors, such as hypertension, diabetes, obesity, and smoking, for CVDs were rarely found in lupus patients. Therefore, our results indicated that the dyslipidemia observed in these women was associated with SLE, which differed from what has been seen in the general population of women residing in Bahia and not afflicted with this autoimmune disease [20]. The lipid profile of patients belonging to the two SLE groups showed differences in non-HDL-C and TG levels. The superiority of the use of non-HDL-C levels in conjunction with LDL-C levels for predicting cardiovascular events has been documented in several population studies and adopted in the National Cholesterol Education Program, Adult Treatment Panel III [21]. Additionally, this method has been used by international bodies, such as the American Diabetes Association and the American College of Cardiology, involved in CVD prevention and treatment [22]. We found a positive correlation between the levels of non-HDL-C and lupus activity as measured by SLEDAI-2K, indicating the involvement of this atherogenic lipid in SLE pathology and progression.

There is evidence indicating an inverse relationship between increased HDL-C levels and a low prevalence of CVDs, which is related to the role of this lipid particle in preventing LDL-C oxidation [23]. However, this protective function might be compromised in some autoimmune diseases, such as rheumatoid arthritis and SLE, due to the presence of dysfunctional HDL, which exhibits proinflammatory activity and facilitates LDL oxidation [24, 25].

Dyslipidemic lupus patients showed an increase in apoB:apoA ratio. Increased apoB:apoA ratio is associated with cardiovascular risk and represents a predictor of mortality related to coronary heart disease [26]. Additionally, an elevated TG:HDL-C ratio (> 4.0) was observed in 22/69 (32%) dyslipidemic patients, suggesting a higher risk of CVD in these subjects [27]. Here, prior cardiovascular events, including

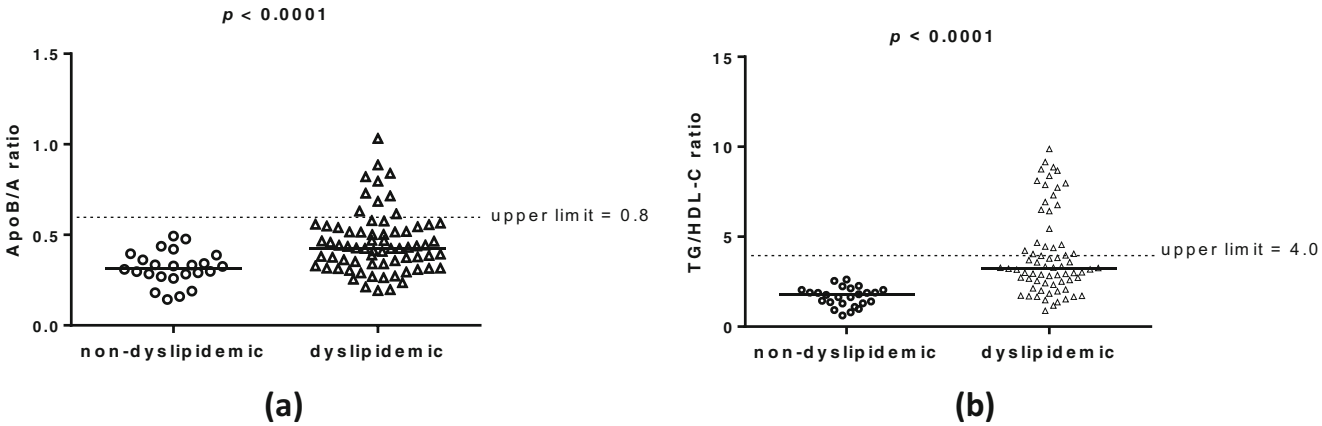

Fig. 1 ApoB:ApoA and TG:HDL-C ratios (**a** and **b**, respectively) in SLE patients without dyslipidemia (non-dyslipidemic; $n = 25$) and SLE patients having dyslipidemia (dyslipidemic; $n = 69$). An ApoB:ApoA ≥ 0.8 and TG:HDL-C ≥ 4.0 are associated with high atherogenic risk. Groups were compared using the Kruskal–Wallis test and Dunn's post hoc test

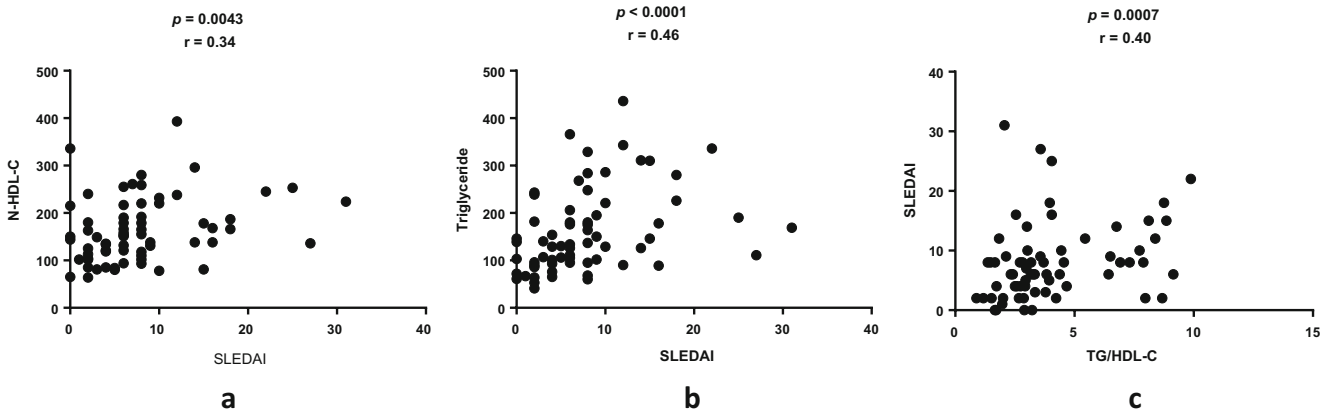

Fig. 2 Correlation between non-HDL-C levels, triglyceride levels, and TG/HDL-C ratio and SLE activity scored by SLEDAI-2K (**a**, **b**, and **c**, respectively) in SLE patients with dyslipidemia ($n = 69$) according to the Spearman rank test

Table 3 Immunological findings in female SLE patients with and without dyslipidemia

Component lipid (mg/dL)	Non-dyslipidemia ($n = 25$)	Dyslipidemia ($n = 69$)	p
ANA	160 (40–640) (23/25)	640 (160–1280) (64/69)	0.008
dsDNA Ab	99 (56–219) (13/25)	239 (81–280) (41/69)	> 0.05
Nucleosome Ab	70 (31–185) (23/25)	164 (51–200) (61/69)	> 0.05
Sm Ab	69 (47–214) (6/25)	61 (42–314) (21/69)	> 0.05
SS-A/Ro Ab	71 (42–133) (7/25)	81 (53–176) (29/69)	> 0.05
SS-B/La Ab	25 (1/25)	80 (33–176) (10/69)	ND
RNP/Sm Ab	118 (99–244) (9/25)	99 (82–207) (30/69)	> 0.05
Rib-P Ab	23 (13–228) (6/25)	18 (15–161) (15/69)	> 0.05
IgA anti-β2GPI	17 (11–22) (4/25)	27 (24–36) (15/69)	0.012
IgG anti-β2GPI	Negative (0/25)	24 (15–42) (9/69)	ND
IgM anti-β2GPI	Negative (0/25)	22 (13–53) (5/69)	ND
IgA aCL	Negative (0/25)	27 (15–40) (2/69)	ND
IgG aCL	Negative (0/25)	27 (14–56) (6/69)	ND
IgM aCL	Negative (0/25)	36 (13–62) (3/69)	ND
C3 (mg/dL)	96.7 ± 30.7	88.6 ± 33.8	> 0.05
C4 (mg/dL)	15.4 ± 6.4	15.2 ± 9.1	> 0.05

The number of patients harboring specific autoantibodies in the two groups. Titers [median and IQR (Q1–Q3)] are shown. aCL, anticardiolipin antibodies; ND, not determined

aCL anticardiolipin antibodies, *ND* not determined

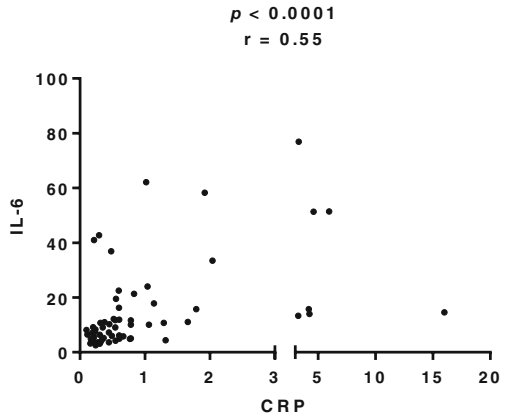

Fig. 3 Correlation between serum IL-6 and CRP levels in SLE patients with dyslipidemia ($n = 61$) according to the Spearman rank test

ischemic stroke and AMI, were reported exclusively by patients in the dyslipidemic group, confirming their relationship with dyslipidemia.

The prevalence and levels of autoantibodies against relevant cell antigens, such as Sm, SS-A/Ro, SS-B/La, Sm/RNP, nucleosome, and Rib-P, were similar between the two groups; but the ANA titer was higher in the dyslipidemia group. Positivity for ANAs and their association with atherosclerosis was previously reported. In one study, the nucleolar pattern observed in the results of an indirect fluorescent antibody test was associated with the presence of atherosclerosis [28], whereas The Cardiovascular Risk in Young Finns study conducted in Finland reported an association between the presence of ANA and the reduction in elasticity of the carotid artery, suggesting that the production of these antibodies might be involved in the development of early or subclinical atherosclerosis [29].

A higher proportion of patients harboring aPLs was observed in the dyslipidemia group, which showed higher levels of IgA anti-β2GPI and suggested that such antibodies might contribute to dyslipidemia in SLE patients. Although these aPLs have been associated with atherogenesis and cardiovascular events [30, 31], we did not find an association between these antibodies and prior AMI or stroke.

SLE is an autoimmune disease that presents significant immune dysregulation, documented by the hyperactivation of B lymphocytes, and a high production of proinflammatory cytokines, such as IL-6 and TNF-alpha [32–34]. These cytokines are involved in the immunology of atherosclerosis, where IL-6 and TNF-α represent atherogenic cytokines that induce the expression of acute-phase atherogenic proteins, such as CRP. By contrast, IL-10 is an immunoregulatory cytokine also detected at increased levels in SLE patients and exhibiting a protective role in atherosclerosis [32–40].

In this study, we observed no differences in serum levels of these cytokines between the two groups of lupus patients. Interestingly, CRP levels were also similar in both groups, although they were much lower than those observed in dyslipidemic women without SLE living in Bahia [20]. Here, an important correlation was observed between IL-6 and CRP levels, but only in the dyslipidemia group, highlighting the likely involvement of this cytokine in the process of atherogenesis in SLE. In contrast to what was observed in dyslipidemic women without SLE living in Salvador [20], TNF-α levels were not elevated in lupus patients presenting dyslipidemia. However, TNF-α is a proinflammatory cytokine associated with SLE and whose roles in the clinical manifestations of this disease remain under investigation [32]. Conversely, one would expect a decrease in IL-10 levels in lupus patients with dyslipidemia based on reports of low IL-10 levels in patients presenting cardiovascular events [39, 40]. However, an increase in serum IL-10 levels has been described in lupus patients and associated with B lymphocyte hyperactivation and autoantibody production [33]. Therefore, our findings suggested that dyslipidemia might downregulate IL-10 production in lupus patients with this metabolic disorder.

In conclusion, we demonstrated a high prevalence of dyslipidemia in Brazilian women with SLE living in Bahia (Brazil) according to their elevated levels of non-HDL-C and increased TG:HDL-C ratios, which suggest a high risk of CVD susceptibility. Immunologic changes are represented in these dyslipidemic SLE patients by high levels of ANAs and a higher production of IgA anti-β2GPI; however, determination of their involvement in the progression of atherosclerosis requires further study.

Table 4 Cytokine levels in SLE patients with and without dyslipidemia

Cytokine (pg/mL)	Without dyslipidemia ($n = 25$)	Dyslipidemia ($n = 69$)	p
IL-6	8.2 (4.0–19.7) (22/25)	10.1 (5.4–16.0) (61/69)	> 0.05
IL-10	6.7 (3.9–9.1) (22/25)	6.5 (5.1–10.5) (65/69)	> 0.05
TNF-α	12.7 (6.3–22.9) (18/25)	10.7 (6.1–26.4) (41/69)	> 0.05

Cytokine levels are expressed as median and IQR (25–75%). The groups were compared using the Mann–Whitney U test. Total no. of patients having detectable serum cytokine levels are shown in parentheses

Funding Conselho Nacional de desenvolvimento Científico e Tecnológico (CNPQ), Grant 306.097/2010-9

Compliance with ethical standards

The study was approved by the Ethics Committee of the Bahia School of Medicine and Public Health.

Disclosures None.

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