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ORIGINAL ARTICLE

Metabolic syndrome in Sjögren's syndrome patients: a relevant concern for clinical monitoring

Kristopherson Lustosa Augusto[1] · **Eloisa Bonfa**[1] · **Rosa Maria Rodrigues Pereira**[1] · **Cleonice Bueno**[1] · **Elaine Pires Leon**[1] · **Vilma Santos Trindade Viana**[1] · **Sandra Gofinet Pasoto**[1,2]

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Abstract Metabolic syndrome (MetS) has been described in autoimmune diseases. However, there are scarce data about MetS and adipocytokine profile in primary Sjögren's syndrome (pSS). Seventy-one female pSS patients (American-European Consensus Group Criteria, 2002) aged 18–65 years and 71 age-, race-matched control women were enrolled in this case–control study. Clinical data were collected by a standardized protocol. Blood levels of glucose, cholesterol, low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), triglycerides, interleukin-1beta (IL-1beta)/IL-6, B-cell activating factor (BAFF), insulin, and leptin/adiponectin/visfatin/resistin were determined. Patients and controls were comparable regarding body mass index (BMI), smoking, sedentariness, and menopause ($p>0.05$). MetS (39.4 vs. 16.9 %, $p=0.005$), hypertension ($p=0.004$), and dyslipidemia ($p=0.002$) were more frequent in patients than controls. IL-1beta, IL-6, BAFF, resistin, and adiponectin levels were higher in patients than controls ($p<0.05$). pSS patients with MetS ($n=28$) had higher BMI, waist circumference, cholesterol, LDL-C, triglycerides, insulin, leptin and HOMA-IR values, and greater hypertension and diabetes rates than pSS patients without MetS ($n=43$) ($p<0.05$). Current and/or previous prednisone use (75.0 vs. 62.8 %, $p=0.313$), current (3.0±4.5 vs. 1.6±3.2 mg/day, $p=0.299$), and cumulative prednisone doses ($p=0.495$) were similar in both groups. Otherwise, IL-1beta level was higher in MetS patients than in non-MetS patients ($p=0.012$), and this finding was confirmed ($p=0.048$) by multivariate analysis with adjustments for age, ethnicity, prednisone use, current and cumulative prednisone doses, and duration of use. We identified high MetS frequency and abnormal adipocytokine profile in pSS. The association of MetS with elevated IL-1beta level suggests that inflammation plays an important role in its pathogenesis.

Keywords Adipocytokines · Cardiovascular risk factors · Insulin resistance · Interleukin-1beta · Metabolic syndrome · Sjögren's syndrome

✉ Sandra Gofinet Pasoto
sandra.pasoto@hc.fm.usp.br

[1] Rheumatology Division, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (USP), São Paulo, Brazil

[2] Faculdade de Medicina da Universidade de São Paulo, Av. Dr. Arnaldo, 455, 3° andar (Disciplina de Reumatologia), sala 3192, Cerqueira César, São Paulo, SP ZIP code 01246-903, Brazil

Introduction

Primary Sjögren's syndrome (pSS) is an autoimmune disease mainly characterized by inflammatory involvement of the exocrine glands leading to dry eye and dry mouth. However, multiple organ systems may be affected, causing a broad spectrum of extraglandular manifestations, such as polyarthritis, cutaneous vasculitis, peripheral neuropathy, small airway disorders, interstitial nephritis, glomerulonephritis, optic neuritis, multiple sclerosis-like disease, and an increased risk of developing lymphoma [1]. pSS predominantly affects females (9:1), with a peak incidence between 40 and 60 years, and its prevalence in the general population ranges from 0.1 to 0.6 % [2].

pSS patients have an inadequate immune response with T and B cell activation and subsequent lymphocytic inflammatory infiltration in target tissues. These cells produce several proinflammatory cytokines, such as interleukin-1beta (IL-1β) and IL-6 [3], which play crucial roles in the development and perpetuation of inflammatory phenomena in pSS [4]. Increased levels of B-cell activating factor (BAFF) have been

detected in the salivary glands, saliva, and sera of pSS patients [5]. Under BAFF stimulation, B cells produce multiple autoantibodies, such as anti-Ro/SS-A and anti-La/SS-B [4].

Studies evaluating patients with other systemic autoimmune inflammatory diseases, particularly rheumatoid arthritis (RA) [6] and systemic lupus erythematosus (SLE) [7], have demonstrated that a perpetuated inflammatory process may play a role in the development of other associated comorbidities, such as hypertension, dyslipidemia, diabetes mellitus, and metabolic syndrome (MetS) [8]. This syndrome consists of a clustering of several cardiovascular risk factors, including hypertension, diabetes, obesity, and dyslipidemia, of which insulin resistance and visceral obesity have been recognized as the most important pathogenic factors [9]. Recently, greater serum levels of adiponectin, leptin, visfatin, and ghrelin have been found in SLE patients [10]. These adipocytokines have important effects on inflammation, glucose homeostasis, and atherosclerosis [11].

There are some data about cardiovascular risk factors associated with pSS. Increased rates of hypertension, dyslipidemia, diabetes, and hyperuricemia have been reported [12, 13]. Recently, multicentric studies have confirmed high frequencies of hypertension [14, 15], hypertriglyceridemia [14], and hypercholesterolemia [15] in these patients. However, there are scarce data about MetS and adipocytokine profile in pSS. In this regard, increased serum levels of adiponectin have been observed in a small sample (n=7) of pSS patients [16]. Thus, the aim of the present study was to evaluate the frequency of MetS and the blood profile pattern of adipocytokines in pSS patients, as well as their possible correlations with proinflammatory cytokines, disease activity, and treatment features.

Patients and methods

Patient group Seventy-one out of 93 female pSS patients (76.3 %) diagnosed according to the international classification criteria for pSS (the American-European Consensus Group Criteria, 2002) [17], aged 18 to 65 years, and followed at the Sjögren's Syndrome Outpatient Clinic, Rheumatology Division, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP) were recruited from May 2011 to January 2013 for a case–control study. This is a tertiary referral University Hospital. The exclusion criteria were positive serological tests for hepatitis B, C, and HIV; the presence of other associated autoimmune diseases, including systemic lupus erythematosus, systemic sclerosis, polymyositis/dermatomyositis, rheumatoid arthritis, and mixed connective tissue disease; the presence of sarcoidosis, head and neck radiation, and graft-versus-host disease, and the use of medications associated with sicca syndrome [17]. The recruited patients agreed to participate in the study and signed an informed consent form. The study was approved by the local ethics committee (#0004/11).

Control group Seventy-one age- and race-matched female volunteers without autoimmune/infectious diseases or sicca symptoms and who agreed to participate and signed the informed consent form were enrolled. They were selected from employees of the Hospital and their family members.

Clinical evaluation of pSS patients Clinical data, including cardiovascular risk factors, were collected through a standardized protocol at study entry. This protocol was composed of a medical interview, physical examination, complementary laboratory tests, and review of an electronic chart database. This electronic chart database has been established in 2001, and it was carried out at 1–6-month intervals to evaluate the clinical features, including those relevant to this study. Patients were systematically evaluated for pSS-related glandular and extraglandular manifestations (constitutional, lymphadenopathy, cutaneous, articular, respiratory, cardiovascular, renal, central, and peripheral nervous system involvements). Previous and current treatments were also recorded, including current and cumulative prednisone doses and duration of use. The classic cardiovascular risk factors including hypertension (systemic hypertension was defined as a systolic blood pressure ≥130 mmHg and/or a diastolic blood pressure ≥85 mmHg and/or by the current use of antihypertensive medications), diabetes mellitus (fasting glucose ≥126 mg/dL and/or the current use of insulin and/or oral hypoglycemic agents), dyslipidemia (high-density lipoprotein-cholesterol [HDL-C]< 50 mg/dL and/or triglycerides≥150 mg/dL and/or current treatment with lipid-lowering drugs), obesity (body mass index [BMI]≥30 kg/m^2), waist circumference (WC), and smoking status were recorded [18]. Sedentary lifestyle was defined as the lack of participation in one or more of the following activities five or more times per week: walking, jogging, bike riding, swimming, aerobics, dancing, calisthenics, gardening, or weight lifting [19].

Clinical evaluation of control individuals At inclusion, cardiovascular risk factors were evaluated in the control individuals according to the same standardized protocol.

Definition of metabolic syndrome MetS was classified according to the Joint Interim Statement of the International Diabetes Federation (IDF) 2009 criteria [18]. This harmonizing statement has been established by the IDF Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. According to this statement, MetS is defined as the presence of three or more of the following five criteria: (1) elevated waist circumference

using population/country specific thresholds (≥80 cm for South American women); (2) elevated triglycerides (≥150 mg/dL) or drug therapy for hypertriglyceridemia; (3) reduced HDL-cholesterol (<50 mg/dL) in females or drug therapy for reduced HDL-C; (4) elevated blood pressure (systolic≥130 and/or diastolic≥85 mmHg) or drug therapy for hypertension; and (5) elevated fasting glucose (≥100 mg/dL) or drug therapy for hyperglycemia [18].

Disease activity score At study inclusion, disease activity was determined according to the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) [20].

Blood collection, laboratory testing and storage Blood samples from all patients and controls were obtained after 12 h of overnight fasting at study entry for the determination of serum levels of glucose, total cholesterol, high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), very-low-density lipoprotein-cholesterol (VLDL-C), triglycerides (TG), proinflammatory cytokines, interleukin-1beta (IL-1β) and IL-6, B-cell activating factor (BAFF), insulin, the adipocytokine profile (adiponectin, leptin, visfatin, and resistin), total ghrelin, and plasminogen activator inhibitor-1 (PAI-1). For the measurement of cytokines, insulin, adipocytokines, ghrelin, and PAI-1, blood samples were immediately placed on ice and centrifuged under refrigeration to obtain serum samples, which were stored at −80 °C until use. These determinations were performed in all sera simultaneously.

Lipid profile Total cholesterol, HDL-C, and triglycerides in the serum samples were measured enzymatically by the colorimetric method with a Modular P chemistry analyzer (Roche Diagnostics, Mannheim, Germany). Levels of VLDL-C and LDL-C were estimated because all samples had TG levels <300 mg/dL. VLDL-C levels were calculated using the ratio TG/5, and LDL-C levels were determined based on the following equation: LDL-C=total cholesterol—(HDL-C+VLDL-C) [21].

Determination of serum levels of IL-1β, IL-6, and BAFF Serum levels of IL-1β and IL-6 were measured by a multiplex cytokine array system as previously described [22] and following the manufacturer's instructions (LuminexxMAP, EMD Millipore Corporation, Darmstadt, Germany). The assay sensitivities (minimum detectable concentrations [minDC] in pg/mL) and the intra-assay coefficients of variation (CV, %) were 0.1 pg/mL and 7.5 % for IL-1β and 1.6 pg/mL and 7.8 % for IL-6, respectively. Serum BAFF concentrations were determined by the enzyme linked immunosorbent assay (ELISA) as outlined elsewhere [5] (USCN Life Science, Wuhan, China). The minDC and intra-assay CV were <0.058 ng/mL and <10 %, respectively.

Determination of serum levels of insulin, adipocytokines, and total ghrelin Serum concentrations of insulin, adiponectin, leptin, visfatin, resistin, PAI-1, and total ghrelin were measured with a Luminexx MAP technology using a multiplex suspension array system (EMD Millipore Corporation, Darmstadt, Germany), as previously described [23] and according to the manufacturer's instructions. The minDC and intra-assay CV were 52 pg/mL and 3 % for insulin, 0.04 ng/mL and 3 % for leptin, 0.15 ng/mL and 5.6 % for adiponectin, 0.007 ng/mL and 6.0 % for resistin, 0.001 ng/mL and 6.6 % for PAI-1, and 2 pg/mL and 3 % for total ghrelin. Serum visfatin levels were determined by ELISA as outlined elsewhere [24] (USCN Life Science, Wuhan, China). The minDC and intra-assay CV were <6.3 pg/mL and <10 %, respectively.

Insulin resistance For the evaluation of insulin resistance, the homeostasis model assessment index (HOMA-IR) was calculated according to the formulas in HOMA model 21 [25].

Evaluation of body fat mass Body fat mass percentage was assessed by dual-energy x-ray absorptiometry (DXA) (Hologic QDR-4500 Discovery, Hologic Inc., Waltham, USA).

Statistical analysis The data were analyzed using SPSS version 12.0. Comparisons between two groups (pSS patients vs. control individuals and pSS patients with MetS vs. pSS patients without MetS) were conducted using Student's *t* test or the Mann–Whitney *U* test for continuous variables and the chi-squared test or Fisher's exact test for categorical variables when applicable. Multivariate analysis with adjustments for age, ethnicity, prednisone use, current and cumulative prednisone doses, and duration of use was performed to compare the MetS patients with the non-MetS patients by analysis of covariance. Linear correlations between several variables (two by two) were evaluated by the Pearson correlation coefficient (values above 0.7 indicated a strong correlation, values of 0.5 to 0.7 suggested a moderate correlation, and those below 0.5 indicated a low correlation). Associations between IL-1β level and MetS criteria, IL-1β and insulin, and IL-β and HOMA-IR with adjustment for age were evaluated by Pearson coefficient with partial correlation analysis. The results are shown as a proportion or the mean±standard deviation (SD). Only two-tailed tests were applied. A p value<0.05 was considered to be statistically significant.

Results

Comparative analysis between pSS patients and control individuals The patients and control individuals were similar regarding to mean age (47.6±10.3 vs. 47.2±10.3 years, p= 0.833), ethnicity (white individuals; 77.5 vs. 77.5 %, p=

1.000), body mass index (BMI) (27.6±6.4 vs. 26.7±3.6 kg/m^2, p=0.783), smoking (p=1.000), and sedentary lifestyle (p=0.847) (Table 1). No patient or control had a history of alcohol abuse. The frequency of menopause status (p=0.502) and the use of hormonal replacement therapy (p=1.000) were also comparable in both groups (Table 1).

High prevalences of MetS (39.4 vs. 16.9 %, p=0.005) and hypertension (32.4 vs. 11.3 %, p=0.004) were observed in the patients compared with the control group. Waist circumference (87.4±13.3 vs. 84.8±9.4 cm, p=0.181) and body fat mass (36.1±6.7 vs. 34.7±4.3 %, p=0.155) were comparable in both groups. In contrast, the frequencies of dyslipidemia (22.5 vs. 4.2 %, p=0.002) and use of statins (19.7 vs. 4.2 %, p=0.008) were greater in the pSS patients, and there was a trend towards lower HDL-C levels in this group (54.8±16.2 vs. 59.7±14.3 mg/dL, p=0.058) (Table 1). No differences were observed in the glycemia (p=0.062) (Table 1), insulin levels (p=0.271), or HOMA-IR (p=0.662) (Table 2). The serum levels of IL-1β (37.8±124.1 vs. 1.1±1.1 pg/mL, p=0.008), IL-6 (40.5±114.4 vs. 4.6±8.1 pg/mL, p<0.0001), BAFF (0.19±0.56 vs. 0.01±0.02 pg/mL, p<0.0001), resistin (13.3±6.9 vs. 8.7±5.3 ng/mL, p<0.0001), and adiponectin (27,411.8±16,096.2 vs. 22,316.3±22,639.6 ng/mL, p=0.001) were higher in the patients than in the controls (Table 2). The levels of leptin, visfatin, and ghrelin were comparable in both groups (p>0.05) (Table 2).

Comparison between pSS patients with and without metabolic syndrome The 28 patients with MetS and 43 patients without MetS were comparable regarding demographic characteristics (Table 3). In contrast, the former group had greater values of BMI, waist circumference, body fat mass, systolic and diastolic blood pressure, total cholesterol, LDL-C, VLDL-C and triglycerides, and higher frequencies of hypertension and diabetes (p<0.05) (Table 3). In addition, the MetS patients presented higher levels of insulin and leptin (p<0.05) (Table 4).

Table 1 Comparative analysis between pSS patients and healthy individuals on demographic characteristics, cardiovascular risk factors, and frequency of metabolic syndrome[a]

	pSS n=71	Healthy individuals n=71	p value
Age (years)	47.6±10.3	47.2±10.3	0.833
Female gender	71 (100)	71 (100)	1.000
White race	55 (77.5)	55 (77.5)	1.000
Metabolic syndrome	28 (39.4)	12 (16.9)	0.005
BMI (kg/m^2)	27.6±6.4	26.7±3.6	0.783
Waist circumferences (cm)	87.4±13.3	84.8±9.4	0.181
Body fat mass (%)	36.1±6.7	34.7±4.3	0.155
Hypertension	23 (32.4)	8 (11.3)	0.004
Blood pressure			
Systolic (mmHg)	123.5±18.9	113.2±10.7	0.001
Diastolic (mmHg)	79.2±13.8	74.4±10.1	0.090
Diabetes mellitus	4 (5.6)	2 (2.8)	0.681
Glycemia (mg/dL)	81.5±11.9	85.6±13.9	0.062
Dyslipidemia	16 (22.5)	3 (4.2)	0.002
Cholesterol (mg/dL)	178.0±39.8	187.8±49.8	0.043
HDL-cholesterol (mg/dL)	54.8±16.2	59.7±14.3	0.058
LDL-cholesterol (mg/dL)	102.4±32.2	116.3±35.2	0.015
VLDL-cholesterol (mg/dL)	21.0±9.0	20.0±9.1	0.489
Triglycerides (mg/dL)	105.0±44.8	100.6±45.2	0.564
Statin use	14 (19.7)	3 (4.2)	0.008
Smoking			
Current	3 (4.2)	2 (2.8)	1.000
Previous	13 (18.3)	17 (23.9)	0.538
Alcoholism	0 (0)	0 (0)	–
Sedentary lifestyle	54 (76.1)	52 (73.2)	0.847
Menopause status	38 (53.5)	33 (46.5)	0.502
Hormone replacement therapy	4 (5.6)	4 (5.6)	1.000

pSS primary Sjögren's syndrome, *n* number of patients, *SD* standard deviation, *BMI* body mass index

[a] The results are expressed as the mean±standard deviation or *n* (%)

Table 2 Comparative analysis between pSS patients and healthy individuals on serum levels of proinflammatory cytokines, B-cell activating factor, and adipocytokines[a]

	pSS n=71	Healthy individuals n=71	p value
Adiponectin (ng/mL)	27,411.8±16,096.2	22,316.3±22,639.6	0.001
Resistin (ng/mL)	13.3±6.9	8.7±5.3	<0.0001
PAI-1 (ng/mL)	57.6±23.4	65.0±27.8	0.087
Leptin (ng/mL)	18.6±12.2	15.8±10.2	0.141
Insulin (pg/mL)	523.9±412.9	440.2±327.9	0.271
Grelin (pg/mL)	52.9±52.5	46.7±39.4	0.928
Visfatin (pg/mL)	656.7±208.9	611.5±127.2	0.468
HOMA-IR	3.0±2.3	2.8±2.9	0.662
IL-1β (pg/mL)	37.8±124.1	1.1±1.1	0.008
IL-6 (pg/mL)	40.5±114.4	4.6±8.1	<0.0001
BAFF (pg/mL)	0.19±0.56	0.01±0.02	<0.0001

pSS primary Sjögren's syndrome, *n* number of patients, *SD* standard deviation, *PAI-1* plasminogen activator inhibitor, *IL-1β* interleukin-1beta, *IL-6* interleukin-6, *BAFF* B-cell activator factor

[a] The results are expressed as the mean±standard deviation or *n* (%)

Regarding pSS manifestations, the frequencies of arthritis (60.7 vs. 39.5 %, p=0.094), cutaneous vasculitis (25 vs. 18.6 %, p=0.562), Raynaud's phenomenon (42.9 vs. 23.3 %, p=0.115), small airway disease (17.9 vs. 20.9 %, p=1.000), renal tubular acidosis (7.1 vs. 9.3 %, p=1.000), and central or peripheral nervous system involvement (17.9 vs. 9.3 %, p=0.304) were comparable between the pSS patients with and without metabolic syndrome. The disease duration and disease activity score at inclusion were also similar between both groups (p>0.05) (Table 3).

Current and/or previous prednisone use (75.0 vs. 62.8 %, p=0.313), current (3.0±4.5 vs. 1.6±3.2 mg/day, p=0.299), and cumulative prednisone doses (p=0.495) were similar in both groups (Table 3). Otherwise, IL-1β level was higher in MetS patients than in non-MetS patients (83.1±187.6 vs. 8.4 ±27.7 pg/mL, p=0.012) (Table 4).

Multivariate analysis of pSS patients with and without metabolic syndrome with adjustments for age, ethnicity, prednisone use, current and cumulative prednisone doses, and duration of use The patients with metabolic syndrome (n=28) and without metabolic syndrome (n=43) were also analyzed by multivariate analysis with adjustments for age, ethnicity, prednisone use, current and cumulative prednisone doses, and duration of use. This analysis confirmed that the MetS group had higher values of diastolic blood pressure (p= 0.010), glucose (p=0.045), insulin (p=0.006), HOMA-IR (p= 0.001), LDL-C (p=0.041), VLDL-C (p=0.001), triglycerides (p=0.001), leptin (p=0.008), and IL-1β (p=0.048) than the non-MetS patients. However, there were no significant differences in the values of systolic blood pressure (p= 0.100), BMI (p=0.057), WC (p=0.051), body fat mass (p= 0.088), or cholesterol level (p=0.082) between these two groups.

Assessment of linear correlations between inflammatory cytokines, insulin, HOMA-IR, and adipocytokines in pSS patients For the pSS patients, linear correlations were evaluated (two by two) between the serum levels of IL-1β, IL-6, and BAFF and the concentrations of insulin, adipocytokines, and the HOMA-IR value. A strong correlation between IL-1β and insulin (r=0.790) and moderate correlations between IL-1β and HOMA-IR (r=0.699), as well as between IL-6 and insulin (r=0.622) and IL-6 and HOMA-IR (r=0.572) were observed. Moderate correlations between BMI and leptin (r=0.638) and between waist circumference and leptin (r= 0.638) were also observed.

Assessment of linear correlations with adjustment for age between IL-1β level and MetS criteria, IL-1β and insulin, and IL-β and HOMA-IR in pSS patients Correlations of IL-1β level with each of the individual criteria for MetS were low (waist circumference; r=0.165, triglycerides; r=0.099, HDL-cholesterol; r=−0.107, systolic blood pressure; r= 0.133, and diastolic blood pressure; r=0.104). The analysis with adjustment for age confirmed the strong correlation between IL-1β and insulin (r=0.792), as well as between IL-1β and HOMA-IR (r=0.700).

Assessment of linear correlations between IL-1β/BAFF levels, insulin, HOMA-IR, and adipocytokines in the groups of pSS patients with and without MetS These analyzes confirmed the correlations between IL-1β/insulin (r= 0.891) and IL-1β/HOMA-IR (r=0.778), as well as between IL-6/insulin (r=0.742) and IL-6/HOMA-IR (r=0.678) only in the group of pSS patients with MetS. We also observed a strong correlation between IL-1β/ghrelin (r=0.877) and a moderate correlation between IL-6/ghrelin (r=0.591) only in the group of pSS patients with MetS.

Discussion

The present study revealed a high frequency of metabolic syndrome and an abnormal adipocytokine profile in female pSS patients. In addition, an elevated serum level of IL-1β was observed in the pSS patients with MetS, suggesting that inflammation is important in the pathogenesis of this condition.

The pSS patient group was compared with age- and race-matched healthy women, which is essential for the appropriate analysis of metabolic syndrome. Indeed, the American population observed an elevated prevalence of MetS that was

Table 3 Comparative analysis between pSS patients with and without metabolic syndrome on demographic characteristics, cardiovascular risk factors, and disease features[a]

	pSS with MetS n=28	pSS without MetS n=43	p value
Age (years)	50.0±9.4	46.0±10.7	0.111
Female gender	28 (100)	43 (100)	1.000
White race	23 (82.1)	37 (86.0)	0.773
BMI (kg/m^2)	29.6±6.2	26.3±6.3	0.032
Waist circumference (cm)	91.6±11.6	84.6±13.7	0.028
Body fat mass (%)	38.1±6.1	34.8±6.7	0.046
Hypertension	16 (57.1)	7 (16.3)	0.001
Blood pressure			
Systolic (mmHg)	130.7±22.8	119.1±14.1	0.011
Diastolic (mmHg)	85.7±15.0	74.9±11.2	0.001
Diabetes mellitus	4 (14.3)	0 (0)	0.021
Glycemia (mg/dL)	84.7±14.7	79.4±9.3	0.180
Dyslipidemia	9 (32.1)	7 (16.3)	0.150
Cholesterol (mg/dL)	192.9±37.6	168.2±38.5	0.001
HDL-cholesterol (mg/dL)	53.5±17.5	55.7±15.3	0.588
LDL-cholesterol (mg/dL)	114.5±27.3	94.6±33.0	0.010
VLDL-cholesterol (mg/dL)	26.1±9.7	17.7±6.7	<0.0001
Triglycerides (mg/dL)	130.1±49.2	88.7±33.1	<0.0001
Statin use	8 (28.6)	6 (14.0)	0.221
Smoking			
Current	0 (0)	3 (7.0)	0.273
Previous	6 (21.4)	7 (16.3)	0.755
Alcoholism	0 (0)	0 (0)	–
Sedentary lifestyle	21 (75)	33 (76.7)	1.000
Menopause status	18 (64.3)	20 (46.5)	0.155
Hormone replacement therapy	1 (3.6)	3 (7.0)	1.000
Disease duration (years)	11.5±6.3	10.7±4.5	0.523
ESSDAI	10.8±6.2	9.0±6.1	0.240
Prednisone			
Current and/or previous use	21 (75.0)	27 (62.8)	0.313
Current use	10 (35.7)	10 (23.3)	0.289
Current dose (mg/day)	3.0±4.5	1.6±3.2	0.299
Cumulative dose (g)	6.7±9.2	4.1±4.7	0.495
Duration of use (years)	2.2±2.9	2.2±3.8	0.999
Antimalarials			
Current and/or previous use	24 (85.7)	41 (95.4)	0.204
Current use	14 (50.0)	26 (60.5)	0.466

pSS primary Sjögren's syndrome, *n* number of patients, *SD* standard deviation, *BMI* body mass index, *ESSDAI* EULAR Sjögren's Syndrome Disease Activity Index

[a] The results are expressed as the mean±standard deviation or *n* (%)

correlated with increased age, particularly among women [26]. Furthermore, differences in genetic background, age, and gender distribution may account for the variable MetS prevalence observed among worldwide populations [27]. In addition, the groups of patients and control individuals in this study were similar regarding the frequencies of menopause status and sedentary lifestyle, which have also been associated with metabolic syndrome [28].

We observed higher frequencies of hypertension and dyslipidemia in the pSS patients than the control subjects, despite their comparable BMI and waist circumference values. The control individuals had higher levels of total cholesterol and LDL-C compared with the pSS patients. However, the use of statins was significantly greater in the pSS group compared with the control group, which may explain these findings. Our results confirm previous studies that identified higher

Table 4 Comparative analysis between pSS patients with and without metabolic syndrome on serum levels of proinflammatory cytokines, B-cell activating factor, and adipocytokines[a]

	pSS with MetS n=28	pSS without MetS n=43	p value
Adiponectin (ng/mL)	23,780.6±16,709.9	29,776.3±15,420.8	0.126
Resistin (ng/mL)	12.7±5.7	13.7±7.5	0.538
PAI-1 (ng/mL)	60.3±25.1	55.8±22.4	0.428
Leptin (ng/mL)	23.1±13.2	15.7±10.6	0.011
Insulin (pg/mL)	710.4±530.9	402.4±254.1	0.003
Grelin (pg/mL)	61.6±64.1	47.3±43.2	0.485
Visfatin (pg/mL)	544.8±243.0	630.4±223.9	0.132
HOMA-IR	4.2±2.8	2.2±1.4	0.0002
IL-1β (pg/mL)	83.1±187.6	8.4±27.7	0.012
IL-6 (pg/mL)	70.6±156.8	20.9±70.7	0.073
BAFF (pg/mL)	0.13±0.20	0.23±0.70	0.476

pSS primary Sjögren's syndrome, *n* number of patients, *SD* standard deviation, *PAI-1* plasminogen activator inhibitor, *IL-1β* interleukin-1beta, *IL-6* interleukin-6, *BAFF* B-cell activator factor

[a] The results are expressed as the mean±standard deviation or *n* (%)

prevalences of hypertension [13–15] and dyslipidemia [12–15] in pSS patients.

Our study also revealed that the frequency of MetS was significantly elevated in the pSS patients compared with the control group. This finding is of concern because individuals with MetS have greater risks of developing cardiovascular disease and type 2 diabetes mellitus compared with those without this clinical condition [9]. Indeed, high rates of asymptomatic atherosclerosis [29–31] and cardiovascular events [15, 32] have been reported in pSS patients.

The pSS patients with metabolic syndrome presented higher BMI, body fat mass and waist circumference values, reflecting central obesity, in addition to greater frequencies of hypertension and diabetes and higher concentrations of total cholesterol, LDL-C, VLDL-C, and triglycerides compared with the patients without MetS. Moreover, greater levels of insulin and HOMA-IR were observed in the first subgroup of patients, suggesting the occurrence of insulin resistance [25].

With regard to the possible risk factors for metabolic syndrome in autoimmune diseases, older age, a longer disease duration, a low C3 complement (but not disease activity score), and a history of glucocorticoid use have been shown to be significantly associated with this clinical complication in SLE [33]. In contrast, we did not observe an association of MetS with disease duration, organic involvements, or prednisone use in the pSS patients. This latter finding might be due to the low current (3.0±4.5 and 1.6±3.2 mg/day) and cumulative (6.7±9.2 and 4.1±4.7 g) dosages of prednisone taken by our pSS patients with and without MetS, respectively. In this regard, current (>10 mg daily) and cumulative (27.2±28.5 vs. 17.6±28.3 g) doses of prednisone have been significantly associated with MetS in SLE [34].

Interestingly, the pSS patients with MetS had greater serum levels of leptin and IL-1β than the non-MetS patients, suggesting the importance of this proinflammatory cytokine in the development of metabolic syndrome in pSS. Indeed, chronic inflammation, which is characterized by the production of interleukin-1 and leptin, is associated with visceral obesity and insulin resistance [9]. In this regard, circulating monocytes from individuals with MetS (without associated autoimmune diseases) produce high levels of IL-1β [35]. Of note, leptin has a proinflammatory effect and may play a role in the pathogenesis of systemic autoimmune diseases by stimulating the production of inflammatory cytokines [11, 36]. Furthermore, plasma concentrations of leptin are correlated with adiposity, and hyperleptinemia is considered to be an independent cardiovascular risk factor [37].

In addition, multivariate analysis with adjustments for age, ethnicity, prednisone use, current and cumulative prednisone doses, and duration of use reinforced the findings of higher diastolic blood pressure, glucose, insulin, HOMA-IR, LDL-C, triglycerides, leptin, and IL-1β levels in the pSS patients with MetS than in those without MetS. Therefore, IL-1β seems to be associated with metabolic syndrome in pSS. The additional findings of a strong correlation between IL-1β and insulin levels and a moderate correlation between IL-1β and HOMA-IR observed herein reinforce the potential role of this proinflammatory cytokine in the pathogenesis of MetS in pSS patients. However, the cross-sectional design of the present study precludes a definitive conclusion regarding a casual effect of IL-1β on MetS pathogenesis in pSS.

Some mechanisms may explain the finding of high circulating level of IL-1β in pSS patients. IL-1β secretion by peripheral blood mononuclear cells is increased in these patients [3]. In addition, elevated expression of proinflammatory cytokine high mobility group box chromosomal protein 1 (HMGB-1), a potent stimulator of IL-1β secretion, was detected in infiltrates of mononuclear cells from biopsy samples of minor salivary glands of pSS patients [3]. The inflammasomes, innate immune receptors that regulate the caspase-1 activity and induce inflammation in response to infectious agents and host molecules, possibly also have a pathogenic role in autoimmune disorders such as pSS [38]. The $P2X_7$ receptor ($P2X_7R$) NLRP3 (Nod-like receptor family protein 3) inflammasome complex stimulates the secretion of IL-1β through the activated caspase [38]. Recently, higher expressions of $P2X_7R$ and of the inflammasome components NLRP3 were demonstrated in minor salivary glands from pSS patients than those from non-pSS individuals, suggesting that innate immunity could contribute to the induction of inflammation in pSS [39]. In this regard, a randomized, double blind, placebo-controlled trial of IL-1β blockade in pSS suggested that this treatment could improve fatigue in

pSS patients [40]. However, future studies are needed to evaluate this therapeutic approach in pSS. It is also interesting that inflammasomes have been implicated in the pathogenesis of metabolic disorders (atherosclerosis, type 2 diabetes, and obesity) [38].

Regarding to the strong correlation between IL-1β and ghrelin in group of pSS patients with MetS, it is interesting that in an experimental model, it was observed that, despite the ghrelin stimulate food intake and weight gain, it can also induce mechanisms of cell protection to compensate the effects of systemic inflammatory response [41]. Further studies are needed to evaluate this hypothesis.

Multivariate analysis with adjustments for age, ethnicity, prednisone use, current and cumulative prednisone doses, and duration of use also revealed that the BMI, waist circumference, body fat mass, and total cholesterol levels were comparable in the MetS and non-MetS patients. These findings may indirectly suggest the importance of prednisone in the development of hypercholesterolemia and obesity, as has been previously demonstrated for SLE patients [42].

Our study also demonstrated an abnormal adipocytokine profile in the pSS patients, including elevated serum levels of adiponectin and resistin comparatively with the control individuals. Interestingly, increased serum concentrations of adiponectin have also been observed in other systemic autoimmune inflammatory diseases, such as SLE [10], and in a small sample (n=7) of pSS patients [16]. Adiponectin has anti-diabetic, anti-inflammatory, and anti-atherogenic effects [11]. However, high circulating levels of resistin may lead to deleterious metabolic and proinflammatory effects. In fact, it has been shown that resistin is associated with insulin resistance in rodents and can stimulate the production of proinflammatory cytokines, IL-1β, IL-6, and TNF-α (tumor necrosis factor-alpha) by mononuclear peripheral blood cells in humans [43]. One study has evaluated the serum and salivary levels of this adipocytokine in pSS patients, observing high concentrations only in saliva, and the resistin levels were correlated with the intensity of inflammation in the minor salivary glands [44]. These findings suggest that resistin is potentially involved in the glandular inflammatory process in pSS [44]. Our findings expand upon this notion, suggesting that resistin may also be a systemic inflammatory mediator in pSS. In support of this hypothesis, it has been demonstrated that plasma resistin levels are correlated with inflammatory markers and are predictive of coronary atherosclerosis in humans [45].

Conclusions

In conclusion, our study identified a high frequency of MetS and an abnormal adipocytokine profile in pSS patients. The interesting association of MetS with elevated IL-1β suggests that this proinflammatory cytokine plays an important role in its pathogenesis.

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