High Prevalence of Serum Metabolic Alterations in Primary Sjögren's Syndrome: Influence on Clinical and Immunological Expression

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ABSTRACT. ***Objective.*** To analyze the prevalence and clinical significance of associated metabolic alterations [dyslipidemia, diabetes mellitus (DM), and hyperuricemia] in a large series of unselected patients with primary Sjögren's syndrome (SS).

Methods. We analyzed 254 consecutive patients with primary SS who had a complete analytical followup study for at least 5 consecutive years. The control group consisted of 254 age and sex-matched patients without systemic autoimmune diseases consecutively followed during the same period in a primary care center.

Results. In comparison with controls, patients with primary SS showed a higher frequency of dyslipidemia (47% vs 33%; p = 0.002), DM (28% vs 18%; p = 0.006), and hyperuricemia (9% vs 4%; p = 0.007). The mean age at SS diagnosis was 10 years greater in patients with DM (p < 0.001) and hyperuricemia (p = 0.009). Hypercholesterolemia was associated with a lower frequency of immunological markers such as anti-Ro/SSA antibodies (p = 0.001), anti-La/SSB antibodies (p = 0.005), low C3 (p = 0.047), and low C4 levels (p = 0.030), while hypertriglyceridemia and DM were associated with a higher prevalence of extraglandular features, especially renal, liver, and vasculitic involvement. A higher prevalence of DM was found in patients treated with corticosteroids (40% vs 19%; p = 0.001).

Conclusion. Patients with primary SS showed a higher prevalence of associated dyslipidemia, DM, and hyperuricemia in comparison with an age and sex-matched control group. Metabolic alterations were associated with a differentiated pattern of clinical and immunological SS expression, but not with SS-related therapies (except for the higher frequency of DM observed in patients treated with corticosteroids). (First Release Feb 15 2007; J Rheumatol 2007;34:754–61)

Key Indexing Terms:
HYPERCHOLESTEROLEMIA HYPERTRIGLYCERIDEMIA DIABETES MELLITUS
SJÖGREN'S SYNDROME SERUM METABOLIC ALTERATIONS

Sjögren's syndrome (SS) is a systemic autoimmune disease that presents with sicca symptomatology of the main mucosa surfaces[1]. The main sicca features (xerophthalmia and xerostomia) are determined by specific ocular (Rose-Bengal staining, Schirmer test) and oral (salivary flow measurement, parotid scintigraphy) tests. The histological hallmark is a focal lymphocytic infiltration of the exocrine glands, determined by a biopsy of the minor labial salivary glands[2]. The spectrum of the disease extends from sicca syndrome to systemic involvement (extraglandular manifestations) and may be complicated by the development of lymphoma. Patients with SS present a broad spectrum of analytical features (cytopenias, hypergammaglobulinemia, high erythrocyte sedimentation rate) and autoantibodies, of which antinuclear antibodies (ANA) are the most frequently detected, anti-Ro/SSA the most specific, and cryoglobulins and hypocomplementemia the main prognostic markers[3].

The clinical significance of metabolic alterations in patients with primary SS is little studied, even though there is evidence linking sicca syndrome with dyslipidemia and diabetes. The first reports of a so-called "pseudo-Sjögren syndrome" in patients with hyperlipidemia or hyperlipoproteinemia date from around 1970[4,5]. In addition, a link between SS and diabetes is supported by both experimental (the non-obese diabetic mouse is a murine model of diabetes that develops an exocrine disease similar to human SS) and clinical studies (a high frequency of sicca syndrome in patients with diabetes)[6-8]. In late 2005, 2 case-control studies attempted to link primary SS with cardiovascular and metabolic alterations in small series of patients. Lodde, *et al*[9] described a differentiated lipid

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In memoriam, Dr. Josep Font (1953-2006).

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serum profile in patients with primary SS, while Vaudo, *et al*[10] found a higher rate of subclinical atherosclerosis in female patients with SS studied by femoral and carotid echography.

We analyzed the prevalence and clinical significance of associated metabolic alterations [dyslipidemia, diabetes mellitus (DM), and hyperuricemia] in a large series of unselected patients with primary SS, focusing on the possible association with demographic, clinical, and immunological features and with the therapies administered.

MATERIALS AND METHODS

Between 1994 and 2000, the clinical and immunological features of 336 Spanish patients with primary SS, consecutively followed in the Department of Autoimmune Diseases of the Hospital Clinic (Barcelona, Spain), were characterized following a standardized protocol study[11,12]. All patients fulfilled 4 or more of the 1993 European Classification Criteria for primary SS[13], including either positive immunological markers or salivary lip biopsy as mandatory criteria. Exclusion criteria for the diagnosis of primary SS were the coexistence of other systemic autoimmune diseases, preexisting hematological diseases, and hepatitis B virus, hepatitis C virus or human immunodeficiency virus infections. According to our clinical guidelines, the cohort was prospectively evaluated every 6 months on an outpatient basis, including a routine analytical evaluation of the main biochemical and hematological measures. All these were measured in fasting blood samples using the standard laboratory tests in our hospital and systematically recorded in our database. We reviewed the analytical charts of 254 patients from our cohort (234 female and 20 male, with a mean age at diagnosis of SS of 52.35 ± 0.91 yrs and a mean time of followup of 135.88 ± 3.79 mo) who had a complete analytical study for at least 5 consecutive years after protocol inclusion, excluding missing patients and those with an incomplete clinical or analytical followup.

The control group consisted of 254 age and sex-matched patients without systemic autoimmune diseases consecutively followed during the same period in the primary care center associated with the Hospital Clinic (ABS Les Corts, Barcelona).

Clinical features. Demographic, therapeutic, and clinical data were obtained from medical records from protocol inclusion until the last visit and recorded in our database. Information on therapeutic management included the use of antiinflammatory drugs, antimalarial agents (chloroquine or hydroxychloroquine), corticosteroids, and immunosuppressive agents (cyclophosphamide, azathioprine, or metothrexate). The main clinical manifestations of SS were defined as described[11,12,14].

Serum metabolic alterations. We abstracted the fasting values for total cholesterol, triglycerides, basal glycemia, and uric acid from our database. Hypercholesterolemia was defined as the presence in at least 2 determinations of total cholesterol > 250 mg/dl, hypertriglyceridemia as the presence in at least 2 determinations of triglycerides > 150 mg/dl, DM as the presence in at least 2 determinations of fasting glycemia > 126 mg/dl, and hyperuricemia as the presence in at least 2 determinations of uric acid > 7.4 mg/dl. Patients receiving specific treatments for these processes were considered as having the corresponding metabolic alteration independently of the analytical values obtained during the followup.

Immunological measures. Immunologic tests included ANA determined by indirect immunofluorescence using triple tissue cryostat sections (liver, stomach, kidney) and HEp-2 cells as substrate (Euroimmun), precipitating antibodies to the extractable nuclear antigens Ro/SSA and La/SSB detected by ELISA (Captia, Trinity Biotech, Bray, Ireland), and rheumatoid factor (RF) detected by nephelometry. Serum cryoglobulins were determined as described[15]. Complement measurement consisted of C3 and C4 levels by nephelometry (Behring BNII nephelometer).

Statistical analysis. Categorical data were compared using the chi-square and Fisher's exact tests. Continuous variables were analyzed with Student's t test in large samples of similar variance and with the nonparametric Mann-Whitney U-test for small samples, with results indicated as mean ± standard error of the mean (SEM). A 2-tailed value of $p < 0.05$ was taken to indicate statistical significance. We compared the main demographic, clinical, and immunological SS data of the total cohort according to the presence or absence of the following dichotomized variables: hypercholesterolemia yes/no, hypertriglyceridemia yes/no, DM yes/no, and hyperuricemia yes/no. Due to the frequent association between these metabolic alterations, we also stratified the patients into 5 subgroups according to the presence of each metabolic alteration alone (hypercholesterolemia alone, hypertriglyceridemia alone, hyperglycemia alone, and hyperuricemia alone) or the coexistence of 2 or more metabolic alterations (coexisting metabolic alterations). Each of these 5 subgroups was separately compared with the SS patients with a normal metabolic profile, defined as normal values for total cholesterol, triglycerides, blood glucose, and uric acid. A multiple logistic regression analysis was performed when several variables appeared to have statistical significance in the univariate analysis. The statistical analysis was performed with the SPSS program (SPSS, Chicago, IL, USA).

RESULTS

Of the 254 patients with primary SS, 86 (34%) had hypercholesterolemia, 72 (28%) DM, 70 (28%) hypertriglyceridemia, and 24 (9%) hyperuricemia. Sixty-seven (26%) had 2 or more altered metabolic measures (Table 1). In comparison with the control group, patients with primary SS showed a higher frequency of hypertriglyceridemia (28% vs 17%, $p = 0.004$, odds ratio 1.87, 95% confidence interval 1.19–2.94), DM (28% vs 18%; $p = 0.006$, OR 1.79, 95% CI 1.15–2.79), hyperuricemia (9% vs 4%; $p = 0.007$, OR 2.84, 95% CI 1.24–7.08), and coexisting metabolic alterations (26% vs 18%; $p = 0.025$, OR 1.62, 95% CI 1.04–2.54) (Table 1). An altered metabolic profile, defined by the presence of hypercholesterolemia, hypertriglyceridemia, DM, and/or hyperuricemia, was found in 148 (58%) out of 254 patients with primary SS (Table 1).

Influence of metabolic alterations in SS expression

Hypercholesterolemia. Hypercholesterolemia was found in 86 (34%) patients with primary SS. Comparison of the main demographic and clinical characteristics between patients with normal cholesterol values and those with hypercholesterolemia showed no significant differences. With respect to the immunological profile, patients with hypercholesterolemia had a lower frequency of hypergammaglobulinemia (17% vs 36%; $p = 0.002$), anti-Ro/SSA antibodies (20% vs 40%; $p = 0.001$), anti-La/SSB antibodies (14% vs 30%; $p = 0.005$), low C3 levels (13% vs 24%; $p = 0.047$), and low C4 levels (7% vs 17%; $p = 0.033$). None of these variables reached statistical significance in the multivariate analysis (Table 2). When we compared the characteristics of the 40 patients with hypercholesterolemia alone with the 106 patients with a normal metabolic profile, the differences were statistically significant for the mean age at SS diagnosis (53.0 vs 47.7 yrs; $p = 0.05$) and the prevalence of anti-Ro/SSA antibodies (10% vs 47%; $p < 0.001$), anti-La/SSB antibodies (2% vs 35%; $p < 0.001$), and low C4 levels (5% vs 19%; $p = 0.039$).

Hypertriglyceridemia. Hypertriglyceridemia was found in 70

Table 1. Prevalence of serum metabolic abnormalities in unselected patients with primary Sjögren's syndrome (SS) in comparison with controls without autoimmune diseases.

	Primary SS, N = 254 n (%)	Controls, N = 254 n (%)	Bilateral p	OR 95% CI
Normal metabolic profile	106 (42)	155 (61)	< 0.001	0.46 (0.32–0.66)
Altered metabolic profile	148 (58)	99 (39)	< 0.001	2.19 (1.51–3.17)
Dyslipidemia	120 (47)	85 (33)	0.002	1.78 (1.22–2.59)
Diabetes mellitus	72 (28)	46 (18)	0.006	1.79 (1.15–2.79)
Hyperuricemia	24 (9)	9 (4)	0.007	2.84 (1.24–7.08)
Coexisting alterations	67 (26)	46 (18)	0.025	1.62 (1.04–2.54)

Table 2. Comparison of the main epidemiological, clinical, and immunological features of patients with primary SS according to the presence or absence of hypercholesterolemia.

	Hypercholesterolemia		
	Present, n = 86 n (%)	Absent, n = 168 n (%)	Bilateral p < 0.05
Sex (female)	79 (92)	155 (92)	—
Mean age at SS diagnosis, yrs	54.05 ± 12.62	51.48 ± 15.29	—
Parotidomegaly	22 (26)	30 (18)	—
Articular involvement	40 (46)	80 (48)	—
Raynaud's phenomenon	11 (13)	29 (17)	—
Pulmonary involvement	6 (7)	18 (11)	—
Renal involvement	5 (6)	5 (3)	—
Liver involvement	11 (13)	37 (22)	—
Peripheral neuropathy	4 (5)	14 (8)	—
Vasculitis	5 (6)	12 (7)	—
Autoimmune thyroiditis	14 (16)	24 (14)	—
Hypergammaglobulinemia	13/78 (17)	57/158 (36)	0.022
Antinuclear antibodies	77 (89)	137 (81)	—
Anti-Ro/SSA	17 (20)	67 (40)	0.001
Anti-La/SSB	12 (14)	50 (30)	0.005
Rheumatoid factor	28 (33)	72 (43)	—
Low C3 levels	11 (13)	40 (24)	0.047
Low C4 levels	6 (7)	28 (17)	0.033
Cryoglobulins	6/79 (8)	13/148 (9)	—

(28%) patients with primary SS. Comparison of the main demographic and clinical characteristics between patients with normal triglyceride values and those with hypertriglyceridemia showed a lower prevalence of Raynaud's phenomenon (7% vs 19%; p = 0.021) and a higher frequency of renal involvement (9% vs 2%; p = 0.029), liver involvement (29% vs 15%; p = 0.02), and vasculitis (13% vs 4%; p = 0.023). No significant differences were found with respect to the immunological profile. Raynaud's phenomenon (p = 0.043) and liver involvement (p = 0.03) were significant independent variables in the multivariate analysis (Table 3). When we compared the characteristics of the 13 patients with hypertriglyceridemia alone with the 106 patients with a normal metabolic profile, the differences were statistically significant for the frequency of Raynaud's phenomenon (0% vs 25%; p = 0.038).

Diabetes mellitus. DM was found in 72 (28%) patients with primary SS. Comparison of the main demographic and clinical characteristics between patients with normal blood glucose values and those with DM showed a higher mean age at SS diagnosis (59.9 vs 49.3 yrs; p < 0.001), a lower prevalence of Raynaud's phenomenon (7% vs 19%; p = 0.021), and a higher frequency of pulmonary involvement (21% vs 5%; p < 0.001), renal involvement (8% vs 2%; p = 0.033), liver involvement (35% vs 13%; p < 0.001) and vasculitis (12% vs 4%; p = 0.027). With respect to the immunological profile, patients with DM had a lower frequency of ANA (75% vs 88%; p = 0.014). The mean age at SS diagnosis (p < 0.001) and the presence of liver involvement (p = 0.009) and ANA (p = 0.036) were significant independent variables in the multivariate analysis (Table 4). When we compared the characteristics of the 26 patients with hyperglycemia alone with the 106 patients with a normal metabolic profile, the differences were statistically significant for the mean age at SS diagnosis (62.4 vs 47.7 yrs; p < 0.001), the prevalence of Raynaud's phenomenon (0% vs 25%; p = 0.002), pulmonary involvement (27%

Table 3. Comparison of the main epidemiological, clinical, and immunological features of patients with primary SS according to the presence or absence of hypertriglyceridemia.

	Hypertriglyceridemia		
	Present, n = 70 n (%)	Absent, n = 184 n (%)	Bilateral p < 0.05
Sex (female)	63 (90)	171 (93)	—
Mean age at SS diagnosis, yrs	53.19 ± 11.94	52.03 ± 15.33	—
Parotidomegaly	18 (26)	34 (18)	—
Articular involvement	31 (44)	89 (48)	—
Raynaud's phenomenon	5 (7)	35 (19)	0.021*
Pulmonary involvement	9 (13)	15 (8)	—
Renal involvement	6 (9)	4 (2)	0.029
Liver involvement	20 (29)	28 (15)	0.020*
Peripheral neuropathy	6 (9)	12 (6)	—
Vasculitis	9 (13)	8 (4)	0.023
Autoimmune thyroiditis	10 (14)	28 (15)	—
Hypergammaglobulinemia	18/66 (27)	52/170 (31)	—
ANA	62 (89)	152 (83)	—
Anti-Ro/SSA	21 (30)	63 (34)	—
Anti-La/SSB	17 (24)	45 (24)	—
Rheumatoid factor	25 (36)	75/182 (41)	—
Low C3 levels	13 (19)	38 (21)	—
Low C4 levels	9 (13)	25 (14)	—
Cryoglobulins	7/64 (11)	12/163 (7)	—

* Statistically significant ($p < 0.05$) in the multivariate analysis.

Table 4. Comparison of the main epidemiological, clinical, and immunological features of patients with primary SS according to the presence or absence of diabetes mellitus.

	Diabetes Mellitus		
	Present, n = 72 n (%)	Absent, n = 182 n (%)	Bilateral p < 0.05
Sex (female)	63 (87)	171 (94)	—
Mean age at SS diagnosis, yrs	59.94 ± 11.77	49.35 ± 14.36	< 0.001*
Parotidomegaly	14 (19)	38 (21)	—
Articular involvement	30 (42)	90 (49)	—
Raynaud's phenomenon	5 (7)	35 (19)	0.021
Pulmonary involvement	15 (21)	9 (5)	< 0.001
Renal involvement	6 (8)	4 (2)	0.033
Liver involvement	25 (35)	23 (13)	< 0.001*
Peripheral neuropathy	9 (12)	9 (5)	—
Vasculitis	9 (12)	8 (4)	0.027
Autoimmune thyroiditis	13 (18)	25 (14)	—
Hypergammaglobulinemia	22/68 (32)	48/168 (29)	—
ANA	54 (75)	160 (88)	0.014*
Anti-Ro/SSA	18 (25)	66 (36)	—
Anti-La/SSB	17 (24)	45 (25)	—
Rheumatoid factor	27 (37)	73 (41)	—
Low C3 levels	10 (14)	41 (22)	—
Low C4 levels	8 (11)	26 (14)	—
Cryoglobulins	8/62 (13)	11/165 (7)	—

* Statistically significant ($p < 0.05$) in the multivariate analysis.

vs 5%; p = 0.002), renal involvement (11% vs 0%; p = 0.007), and the frequency of ANA (61% vs 86%; p = 0.010) and low C3 values (8% vs 28%; p = 0.039).

Hyperuricemia. Hyperuricemia was found in 24 (9%) patients with primary SS. Comparison of the main demographic and clinical characteristics between patients with normal uric acid

values and those with hyperuricemia showed a lower frequency of females (75% vs 94%; p = 0.006), a higher mean age at SS diagnosis (59.7 vs 51.6 yrs; p = 0.009), and a higher prevalence of renal involvement (21% vs 2%; p = 0.001). With respect to the immunological profile, no significant differences were found. The sex (p = 0.039) and presence of renal involvement (p < 0.001) were significant independent variables in the multivariate analysis. We did not compare patients with hyperuricemia alone with those with a normal metabolic profile due to the small number of cases.

Patients with 2 or more metabolic alterations. Sixty-seven (26%) patients had 2 or more metabolic alterations. When compared with the 106 patients with a normal metabolic profile, the 67 patients with 2 or more metabolic alterations had a higher mean age at SS diagnosis (55.6 vs 47.7 yrs; p < 0.001), a lower prevalence of Raynaud's phenomenon (9% vs 25%; p = 0.009), and a higher prevalence of renal involvement (9% vs 0%; p = 0.003). With respect to the immunological profile, no significant differences were found except for a lower frequency of positive anti-Ro/SSA (27% vs 47%; p = 0.011). The age at SS diagnosis (p = 0.003) and presence of Raynaud's phenomenon (p = 0.041) were significant independent variables in the multivariate analysis (Table 5).

Influence of therapies in metabolic alterations. We analyzed the association between serum metabolic alterations and the therapies received during followup. No significant differences were found in the prevalence of the different metabolic alterations according to the therapies received (antiinflammatory agents, antimalarial agents, corticosteroids, and immunosuppressive agents) except for DM, which had a lower prevalence in patients treated with antimalarial agents (6% vs 18%; p = 0.015). In contrast, a higher prevalence of DM was found in patients treated with corticosteroids (40% vs 19%; p = 0.001).

Due to the possible contribution of corticosteroid therapy to the altered metabolic profile of our patients, we recalculated the percentage of each metabolic alteration in patients with SS after excluding those who received corticosteroids. In comparison with the control group, patients with SS not treated with corticosteroids showed a higher frequency of an altered metabolic profile (54% vs 39%; p = 0.002), dyslipidemia (47% vs 33%; p = 0.003), hyperuricemia (8% vs 4%; p = 0.045), and coexisting metabolic alterations (27% vs 18%; p = 0.027). The prevalence of diabetes was also higher in SS but was not statistically significant (23% vs 18%; p = 0.239).

DISCUSSION

Ours is the first study to analyze the main metabolic serum markers (total cholesterol, triglycerides, glycemia, and uric acid) in a large series of unselected patients with primary SS. We found a close association between dyslipidemia, diabetes, and hyperuricemia and most demographic, clinical, and immunological features of SS. In addition, the prevalence of these metabolic alterations was higher than in the control population. The possible influence of metabolic alterations on the expression of SS has been indirectly suggested by very recent studies, in which an inverse correlation between immunological markers and cholesterol/high density lipoprotein (HDL) levels was described[9,10]. These studies and our results suggest that the association between metabolic alterations and primary SS may be closer than previously supposed.

Hypercholesterolemia was the most frequent metabolic alteration found in our patients with primary SS. The associa-

Table 5. Comparison between patients with primary SS and a normal metabolic profile with those with hypercholesterolemia alone, hypertriglyceridemia alone, diabetes mellitus alone, and those with 2 or more metabolic alterations.

	Normal Metabolic Profile, n = 106	Hypercholesterolemia Alone, n = 40	Hypertriglyceridemia Alone, n = 13	Diabetes Mellitus Alone, n = 26	≥ 2 Metabolic Alterations, n = 67
Sex (female)	101 (95)	37 (92)	11 (85)	22 (85)	61 (91)
Mean age at SS diagnosis, yrs	47.66 ± 15.07	53.00 ± 13.09*	50.08 ± 13.37	62.42 ± 13.48*	55.55 ± 11.92*
Parotidomegaly	20 (19)	7 (17)	2 (15)	5 (19)	18 (27)
Articular involvement	56 (53)	18 (45)	4 (31)	9 (35)	32 (48)
Raynaud's phenomenon	27 (25)	7 (17)	0 (0)*	0 (0)*	6 (9)*
Pulmonary involvement	5 (5)	3 (7)	1 (8)	7 (27)*	8 (12)
Renal involvement	0 (0)	1 (2)	0 (0)	3 (11)*	6 (9)*
Liver involvement	17 (16)	2 (5)	2 (15)	8 (31)	19 (28)
Peripheral neuropathy	5 (5)	2 (5)	1 (8)	4 (15)	5 (7)
Vasculitis	5 (5)	1 (2)	1 (8)	1 (4)	8 (12)
Autoimmune thyroiditis	13 (12)	7 (17)	1 (8)	5 (19)	11 (16)
Hypergammaglobulinemia	36/100 (36)	6/35 (17)*	5/12 (42)	8/24 (33)	15/63 (24)
ANA	91 (86)	35 (87)	12 (92)	16 (61)*	58 (87)
Anti-Ro/SSA	50 (47)	4 (10)*	5 (38)	7 (27)	18 (27)*
Anti-La/SSB	37 (35)	1 (2)*	3 (23)	5 (19)	16 (24)
Rheumatoid factor	48 (45)	13 (34)	7 (54)	11 (42)	21 (31)
Low C3 levels	30 (28)	6 (15)	2 (15)	2 (8)*	11 (16)
Low C4 levels	20 (19)	2 (5)*	2 (15)	3 (11)	7 (10)

* Statistically significant (p < 0.05) in comparison with the figures of patients with a normal metabolic profile.

tion between sicca features and lipid disturbances was first reported by Kaltreider and Talal in 1969[4]. Later experimental studies supported the possible role of lipid abnormalities in the etiopathogenesis of primary SS[16,17], while Izumi, *et al*[18] correlated serum cholesterol levels with the salivary function of patients with primary SS. Our results show a strong association between hypercholesterolemia and the immunological expression of primary SS, with an inverse correlation between cholesterol levels and autoantibody production. Lodde, *et al*[9] and Vaudo, *et al*[10], who excluded SS patients with previous cardiovascular and/or metabolic disorders, found similar results. In both studies, the patients with SS had a high frequency of positive immunological markers but lower levels of total cholesterol and HDL compared with control groups. In our study, patients with a normal metabolic profile had a 2-fold higher prevalence of anti-Ro/La antibodies than patients with hypercholesterolemia; these autoantibodies were practically absent in SS patients with hypercholesterolemia alone.

In contrast, hypertriglyceridemia was predominantly related to a differentiated clinical expression of SS rather than to immunological markers. We found a higher prevalence of parotid enlargement in our hypertriglyceridemic patients (26% vs 18%), although the difference was not statistically significant. In 1969, Kaltreider and Talal[4] described 5 patients with hyperlipoproteinemia and bilateral parotid enlargement, of whom only one presented xerostomia, suggesting that sicca features and parotid enlargement do not always coincide in dyslipidemic patients. In 2000, Izumi, *et al*[18] analyzed the main clinical features of 24 patients with a sicca syndrome related to dyslipidemia, including 50 patients with primary SS as a control group. They found parotid gland enlargement in all patients with hypertriglyceridemia, but in none of those with hypercholesterolemia, suggesting a close relationship between parotid gland enlargement and high serum triglyceride levels. The authors concluded that the clinical features, functional studies, specific parotid gland images, and histopathologic features of patients with sicca syndrome related to dyslipidemia were clearly different from those found in patients with primary SS[18].

DM was the second most frequently metabolic alteration in our patients with primary SS, with a frequency 10% higher than that of the control population. This reinforces the association between diabetes and SS reported in experimental and clinical studies[8,19]. In addition, our hyperglycemic patients with SS presented a clearly differentiated pattern of demographic, clinical, and immunological expression. They were older, and had a higher prevalence of the main extraglandular involvements and a lower frequency of positive ANA. In spite of this specific pattern of disease expression, no significant differences were found in the retrospective fulfilment of the 2002 classification criteria between hyperglycemic and normoglycemic patients.

The higher frequency of extraglandular involvement in SS patients with coexisting DM or hypertriglyceridemia suggests that these metabolic alterations might worsen or trigger inflammatory processes in primary SS, contributing to the vascular damage (cutaneous vasculitis, Raynaud's phenomenon, renal involvement) found in patients with primary SS. Recent studies have found chronic vascular inflammation and vasculitis in patients with type 2 diabetes[20,21], while Antonelli, *et al*[22] described a higher prevalence of diabetes in a large series of patients with cryoglobulinemia, suggesting that the association between vasculitis and DM is closer than previously supposed. With respect to liver damage, a finding of diabetes or hypertriglyceridemia in the evaluation of primary SS patients with altered liver profiles may be of some significance due to the association between these metabolic alterations and hepatic steatosis. With respect to hyperuricemia, our hyperuricemic patients with SS were more frequently male and older and had a higher frequency of renal involvement. This suggests that hyperuricemia in primary SS may be related to the demographic profile and to SS-related renal disease.

The close association that we found between serum metabolic alterations and SS expression may give rise to concern about the classification, prognosis, and therapeutic management of patients with primary SS and metabolic alterations. The question arises whether these patients have a true autoimmune-mediated primary SS or a metabolic-mediated disease that mimics primary SS. According to our results, the current 2002 classification criteria are not sensitive to the differences between SS patients with and those without metabolic alterations. These patients may form a specific subset currently classified as primary SS, but with differentiated etiopathogenic mechanisms. With respect to the prognosis, Vaudo, *et al*[10] recently found that subclinical atherosclerosis was evident in about half of a small series of patients with primary SS, although recent studies found that the overall mortality of patients with primary SS was not related to cardiovascular disease[23,24]. However, the possibility of modifying the clinical and immunological expression of primary SS through strict control of the coexisting metabolic alterations seems to be very attractive and has been demonstrated in murine models of SS[17]. Some pharmacological agents used in patients with metabolic syndrome might have a potential role as future treatments in primary SS, including thiazolidinediones, metformin, antioxidants, and statins[25]. Statins have pleiotropic effects that are independent of their lipid-lowering effect, with atorvastatin having a special role as an antiinflammatory and immunomodulatory agent[26,27]. This suggests a promising role for this molecule in the treatment of patients with systemic autoimmune diseases and coexisting metabolic alterations[28].

The prevalence of DM in our patients with primary SS was lower in those treated with antimalarial agents and higher in those treated with corticosteroids. Previous studies in other systemic autoimmune diseases such as systemic lupus erythematosus (SLE) suggested a potential protective role of antimalarial agents in cardiovascular disease and included corti-

costeroid therapy as a cardiovascular risk factor[29]. Our data suggest a potential beneficial role for antimalarial agents in metabolic alterations in patients with primary SS. In contrast, corticosteroid therapy was related to higher prevalence of DM. We suggest limiting the use of corticosteroids in patients with primary SS to treat extraglandular manifestations and using the lowest dose necessary. Higher doses should be reserved for severe or refractory manifestations, with close monitoring of metabolic measures. When longterm corticosteroid therapy is anticipated, the addition of immunosuppresive or biological agents should be considered with the goal of reaching the minimum dose of corticosteroid maintenance therapy.

Our case-control study found a higher frequency of dyslipidemia, diabetes, and hyperuricemia in a large series of patients with primary SS in comparison with an age and sex matched control population. The etiopathogenic basis of this higher prevalence is unclear. Although we did not analyze other metabolic factors that might influence this higher prevalence, such as low density lipoprotein (LDL)-cholesterol or obesity, it is unlikely that patients with primary SS are more obese than the non-autoimmune control population. We analyzed the possible association between this altered metabolic profile and the therapies received by the patients with SS, but found an association only between corticosteroid use and diabetes. It may be hypothesized that the SS itself could cause this altered metabolic profile as a result of the persistent chronic inflammation, or that patients with primary SS may have a specific genetic background that predisposes them to metabolic alterations. Our results suggest possible future lines of research on the posible links between autoimmune and metabolic measures in primary SS. The etiopathogenic role of insulin resistance in the development of metabolic alterations in patients with primary SS may be a promising line of future research, similar to that recently followed in other autoimmune diseases such as SLE[30,31] or rheumatoid arthritis[28,32]. Sada, *et al*[30] have recently described elevated levels of adiponectin in 37 patients with SLE in comparison with healthy controls, while El Magadmi, *et al*[31] found an association between insulin resistance and oxidized LDL in patients with SLE. Insulin resistance may play a role in the etiopathogenesis of patients with primary SS and metabolic alterations.

Patients with primary SS showed a higher prevalence of dyslipidemia, DM, and hyperuricemia in comparison with an age and sex-matched control group. The presence of metabolic alterations was associated with a differentiated pattern of clinical and immunological SS expression. SS-related therapies seem to play a small role, except for the higher frequency of DM observed in patients treated with corticosteroids. Our results suggest that metabolic alterations should be taken into account in the management of patients with primary SS, and that future research on this subject may be of interest.

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