Clinical Rheumatology (2019) 38:2803–2809
https://doi.org/10.1007/s10067-019-04621-2

ORIGINAL ARTICLE

sICAM-1 as potential additional parameter in the discrimination of the Sjögren syndrome and non-autoimmune sicca syndrome: a pilot study

Auksė Zinkevičienė[1,2] · Irena Dumalakienė[1] · Diana Mieliauskaitė[2] · Rita Vilienė[1] · Ieva Narkevičiūtė[1] · Irutė Girkontaitė[1]

Received: 21 February 2019 / Revised: 17 May 2019 / Accepted: 21 May 2019 / Published online: 31 May 2019

Abstract

Objective Both Sjögren's syndrome (SS) and non-autoimmune sicca syndrome (nSS) can show symptoms of dry eyes and a dry mouth, and objective reductions in tear and saliva production. Dry eyes and dry mouth are frequent but they are distinct pathological entities that require diagnostic discrimination.

Methods The aim of present study was to compare the serum levels of sICAM-1, TFF3, RANTES, adiponectin, and FGF in primary (pSS), secondary due to rheumatoid arthritis (sSS), non-autoimmune sicca syndrome (nSS), and healthy groups. The serum levels of selected molecules were determined by enzyme-linked immunosorbent assay (ELISA) in 29 patients with pSS, 30 with sSS, 17 with nSS, and 15 healthy subjects.

Results sICAM-1 was significantly elevated in pSS and sSS patients compared with nSS group. Levels of FGF, TFF3, and RANTES were significantly increased in pSS, sSS, and nSS patients compared with healthy controls. No significant correlations were found between the levels of measured molecules and the clinical parameters.

Conclusions Our study showed that sICAM-1 might be useful as an additional parameter for differential diagnosis of SS and nSS, and TFF could be additional diagnostic marker for SS diagnosis.

Key Points

- *sICAM-1 was significantly elevated in Sjögren syndrome patients compared with non-autoimmune sicca syndrome group.*
- *TFF was significantly elevated in Sjögren syndrome patients compared with healthy controls.*
- *They might be useful as additional parameters for differential diagnosis.*

Keywords FGF · Non-autoimmune sicca syndrome · RANTES · sICAM-1 · Sjögren's syndrome · TFF3

Introduction

Sjögren syndrome (SS) is a progressive multisystem inflammatory disease that primarily affects salivary and lacrimal gland functions and results in the "sicca" complex, a combination of dry eyes and dry mouth. The common histolopathological feature of all organs affected is a potentially progressive lymphocytic infiltration. The pathogenesis of SS includes genetic and environmental factors [1]. Two clinical forms are classically described. Primary SS (pSS) occurs independently of other diseases, and secondary SS (sSS) occurs as a result of another connective tissue disorder [2]. Non-autoimmune sicca syndrome (nSS) is a term which

✉ Auksė Zinkevičienė
aukse.zinkeviciene@gmail.com

[1] Department of Immunology, State Research Institute Centre for Innovative Medicine, Santariškių g. 5, LT-08406 Vilnius, Lithuania

[2] Department of Experimental, Preventive and Clinical Medicine, State Research Institute Centre for Innovative Medicine, Santariškių g. 5, LT-08406 Vilnius, Lithuania

may be used to cover a group of disorders, excluding SS. nSS syndrome occurs when the lacrimal or/and salivary glands are damaged but, unlike SS, nSS is not caused by an autoimmune disorder [3]. Discrimination of these two syndromes is difficult but important as SS is a disease with excess of mortality, mainly related to the systemic involvement of disease and the development of lymphomas in some patients [4]. Both SS and nSS can show the clinical symptoms of dry eyes and a dry mouth, and objective reductions in tear and saliva production are frequent (due to infections and drugs often observed in elderly people) [5]. The autoantigens SSA/Ro and SSB/La are widely used as markers for the diagnosis of SS, which are revealed in approximately 40 to 75% and 23 to 52% of pSS patients, respectively [6–8].

Autoantibodies against α-fodrin have been discussed as an additional biomarker of SS as they have been found in 93% of primary SS patients [9]. However, there is some doubt about the prevalence of α-fodrin autoantigen positivity in SS patients. There are some reports that the sensitivity of immunoglobulin G (IgG) antibodies against α-fodrin for pSS was too low [10, 11].

Elevated serum levels of soluble intercellular adhesion molecule 1 (sICAM-1), CCL5 (RANTES), trefoil factor 3 (TFF3), adiponectin, and fibroblast growth factor (FGF) basic have been noticed in SS patients, but levels of these molecules in patients with SS and nSS have not yet been compared. Additionally, most of the studies have focused on the local expression of sICAM-1, RANTES, and TFF3 in salivary glands.

The aim of the present study was to measure and compare the serum levels of sICAM-1, TFF3, RANTES, adiponectin, and FGF in pSS, sSS due to rheumatoid arthritis, nSS, and healthy groups and to explore possible correlations between the serum levels of these molecules and the clinical parameters of SS activity. This could make it possible to use sICAM-1, TFF3, RANTES, adiponectin, and/or FGF as additional, supporting parameters in the diagnosis and discrimination of the SS and nSS.

Methods

Study group

This study was approved by the Vilnius Regional Biomedical Research Ethics Committee (2014-05-20, No. 158200-14-733-248), and written consent was obtained from each participant. Patients enrolled in the study were recruited from the Rheumatology Center of Vilnius University hospital "Santaros" Clinic. Twenty-nine of these patients had pSS (1 man, 28 women) and 30 had sSS due to RA (2 men, 28 women). One of the groups consisted of 17 women with non-autoimmune sicca syndrome (nSS). None of the patients in this group fulfilled the SS classification criteria and were classified as patients with nSS. The control group consisted of 15 healthy individuals (1 man, 14 women) without previous history of sicca syndrome. The diagnosis of pSS, sSS due to RA, and nSS was firstly established before enrolling in this study. Disease duration (shown in Table 1) is the duration between the first symptoms and diagnosis. The diagnosis of pSS and sSS was based on the inclusion and exclusion criteria as defined in the American-European Consensus Group criteria for Sjögren's syndrome [1]. RA was diagnosed according to the 2010 ACR/EULAR classification criteria for rheumatoid arthritis [12, 13]. Patients in the non-autoimmune sicca syndrome group did not fulfill the SS nor RA classification criteria. Serum samples were collected from both patients and controls after informed consent. No patients were on immunosuppressive medications during this study. Clinical parameters and oral/ocular characteristics of study volunteers are given in Tables 1 and 2.

ELISA

Enzyme-linked immunosorbent assay (ELISA) kits were used for the determination of serum levels of sICAM-1 (DY720, R&D Systems), RANTES (DY278, R&D Systems), FGF (434304, Biolegend), adiponectin (DY1065, R&D Systems), and TFF3 (DY4407, R&D Systems). Measurements were performed according to the manufacturer's instructions.

Statistics

GraphPad Prism software was used for statistical analysis. The differences between not-paired groups were analyzed using a Mann–Whitney *U* test. The correlation was calculated using a Spearman test. The differences were considered to be statistically significant at $p < 0.05$. The analysis of the receiver operating characteristics (ROC) was performed using MedCalc Statistical Software version 18.11.6 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2019).

Results

A total of 91 volunteers were enrolled in the study, and serum levels of sICAM-1, RANTES, adiponectin, FGF, and TFF3 were measured. sICAM-1 was significantly elevated in pSS and sSS patients compared with the nSS group. Levels of FGF, TFF3, and RANTES were significantly ($p < 0.0001$ or $p < 0.001$) increased in pSS, sSS, and nSS patients compared with the healthy controls (Fig. 1), but no difference was seen between the SS and nSS groups. Concentrations of adiponectin in all studied groups were at a similar level. No significant difference was observed in cytokine levels between pSS and sSS patients. Correlations between clinical symptoms and cytokine levels were counted. The levels of FGF correlated weakly positively with the levels of erythrocyte

Table 1 Clinical characteristics of study volunteers

Features	pSS ($n = 29$)	sSS ($n = 30$)	nSS ($n = 17$)
Age in years, mean, (range)	57 (32–77)	60 (49–69)	60 (43–92)
Disease duration (in years, mean ± SD)[a]	7.9 ± 5.0	13.9 ± 9.4	7.94 ± 8.23
Positive autoantibodies			
ANA, *n* (%)	19 (65.52)	7 (23.33)	3 (17.65)
ACCP, *n* (%)	1 (3.45)	19 (63.33)	1 (5.88)
Anti-SSA, *n* (%)	18 (62.01)	4 (13.33)	1 (5.88)
Anti-SSB, *n* (%)	16 (55.17)	2 (6.67)	1 (5.88)
Other parameters			
HgB, (g/l)	132.67 ± 13.67	128.6 ± 13.4	133.27 ± 8.14
PLT, ($\times 10^9$/l)	238.15 ± 47.88	278 ± 66.58	261.46 ± 53.7
WBC, ($\times 10^9$/l)	5.31 ± 1.86	7.75 ± 2.64	6.28 ± 1.42
ESR (mm/h)	30.81 ± 27.17	38.38 ± 23.1	14.6 ± 10.19
CRP (mg/l)	7.6 ± 19.62	15.8 ± 33.19	6.88 ± 14.79

pSS, primary Sjögren's syndrome; *sSS*, secondary Sjögren's syndrome; *nSS*, non-autoimmune sicca syndrome; *ANA*, antinuclear antibodies; *ACCP*, anti-cyclic citrullinated peptide; *HgB*, hemoglobin; *PLT*, platelets; *WBC*, white blood cell; *ESS*, erythrocyte sedimentation rate; *CRB*, C-reactive protein

[a] Disease duration—from the first symptoms (glandular or extraglandular) before diagnosis

sedimentation rate (ESR) ($r = 0.45$, $p < 0.0001$) and weakly negatively with hemoglobin (HgB) ($r = -0.4$, $p < 0.001$). The levels of RANTES correlated weakly negatively with HgB ($r = -0.4$, $p < 0.001$). The levels of adiponectin negatively correlated with the C-reactive protein (CRB) value ($r = -0.36$, $p < 0.001$). No significant correlations were found between the levels of measured molecules and the clinical parameters studied (data not shown).

The ROC curves (Fig. 2) were depicted to determine the area under the ROC curve (AUC) of TFF and FGF in all the patient groups: pSS, sSS, nSS. As we did not obtained significant differences in the serum levels of TFF and FGF between those groups of patients (Fig. 1), we analyzed also all patients together (pSS + sSS + nSS) versus healthy peoples. AUC shows how well the parameter can be distinguished between two diagnostic groups (diseased/healthy). AUC for TFF varied in all groups of patients from 0.929 to 0.965 (Fig. 2, Table 3) with $p < 0.0001$ that shows very good differences between the patients and healthy persons. AUC for FGF varied from 0.751 to 0.763 ($p < 0.0003$). It is also enough to distinguish SS patients from healthy persons.

The ROC curves were used to determine the best cutoff values for TFF and FGF in predicting SS (Table 3). The optimal cutoff values were obtained from the Youden index maximum. The optimal cutoff values for TFF in pSS and sSS patients were > 20.7 ng/ml and > 24.3 ng/ml in nSS patients. The optimal cutoff values for FGF in pSS and sSS patients were > 0 pg/ml and > 133 pg/ml in nSS patients. Based on the data obtained from ROC curves (AUC, cutoff value, sensitivity, specificity, PPV, NPV) is possible to conclude that both serum TFF and FGF could

Table 2 Oral and ocular characteristics of study volunteers

Features	pSS ($n = 29$)	sSS ($n = 30$)	nSS ($n = 17$)	*p* value
Ocular symptoms, mean ± SD	2.34 ± 0.84	1.63 ± 1.28	2.12 ± 0.76	*s/p
Oral symptoms, mean ± SD	1.79 ± 0.66	1.27 ± 0.77	1.06 ± 0.73	**n/p
Duration of dryness in years, mean ± SD	5.8 ± 4.3	4.8 ± 3.9	4.7 ± 6.0	–
Schirmer's I test positive (≤ 5 mm/5 min), *n* (%)	26 (89.66)	28 (93.33)	10 (58.82)	*n/s *n/p
Schirmer's I test (mm/5 min), mean ± SD	3.45 ± 3.29	3.13 ± 2.45	6.18 ± 5.19	
Unstimulated salivary flow positive (≤ 1.5 ml/15 min), *n* (%)	28 (96.55)	14 (46.67)	4 (23.53)	***n/p
Unstimulated salivary flow (ml/15 min), mean ± SD	1.38 ± 0.94	2.05 ± 1.33	2.74 ± 1.36	***n/s ***n/p ***s/p
Focus score (number of lymphocytic foci/4 mm^2), mean ± SD	1.9 ± 0.76	0.89 ± 0.46	0.21 ± 0.41	*s/p

pSS, primary Sjögren's syndrome; *sSS*, secondary Sjögren's syndrome; *nSS*, non-autoimmune sicca syndrome; n/p, nSS versus pSS; n/s, nSS versus sSS; s/p, sSS versus pSS. * $p < 0.05$; ** $p < 0.005$; *** $p < 0.0005$

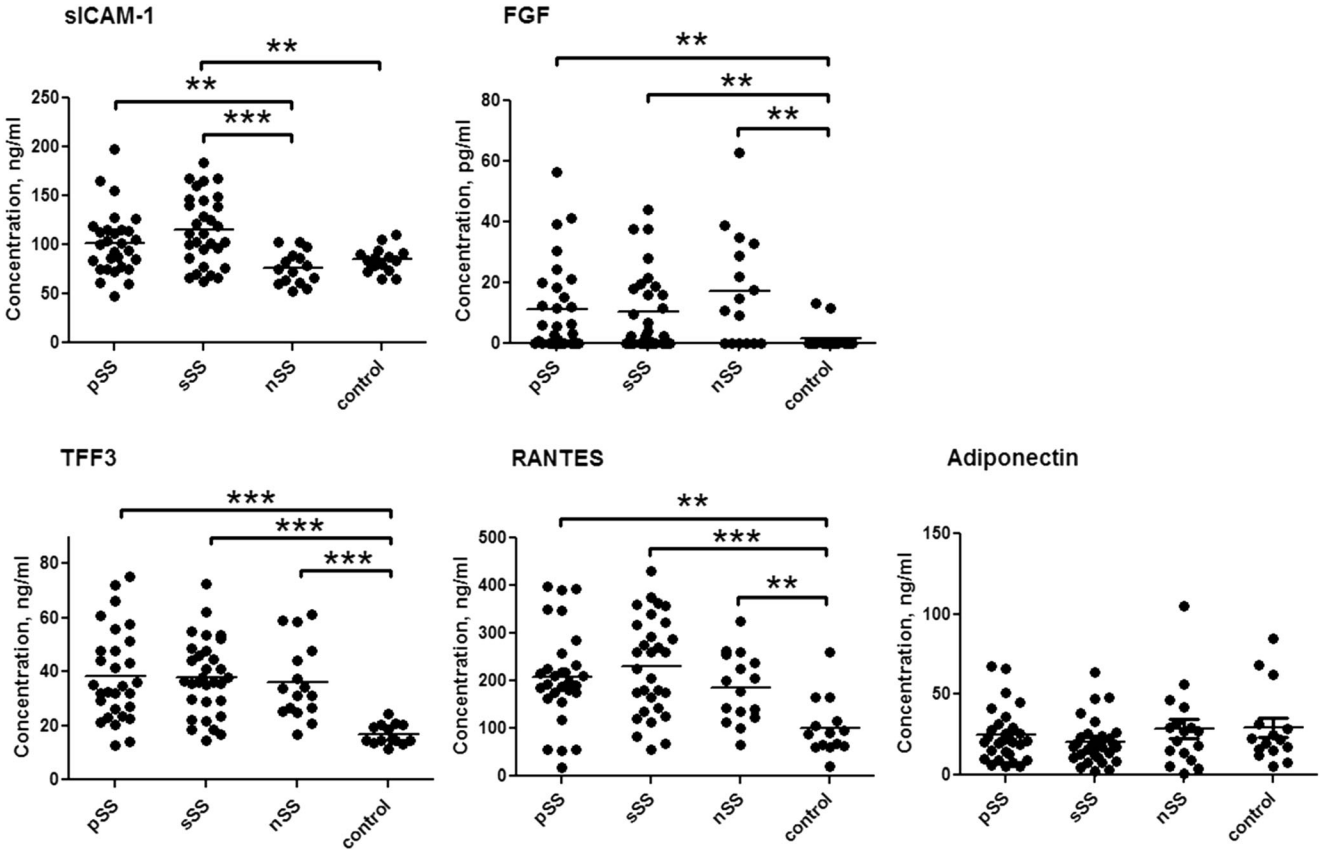

Fig. 1 Comparison of various serum cytokine levels between Sjögren's syndrome (pSS and sSS), non-autoimmune sicca syndrome (nSS) patients, and healthy controls

be additional diagnostic markers; however, TFF has a better diagnostic value compared with FGF.

Discussion

The aims of present study were to compare the serum concentrations of sICAM-1, TFF3, FGF, adiponectin, and RANTES in the pSS, sSS, nSS, and healthy groups and to explore possible correlations between the serum levels of these molecules and the clinical parameters of SS activity.

In our study, the serum levels only of sICAM-1 were elevated in pSS and sSS in comparison with the nSS and healthy control groups. sICAM-1 facilitates various immune responses that require intercellular contact and is involved in migration and co-stimulation of T and B cells. It is known that membrane-bound ICAM-1 is over expressed in SS patients and similar results were obtained in other studies [14–17]. The epithelial cells are the main target in SS, which lead to a deterioration in the functioning of the organs. As SS affects many organs and activation of the epithelial cells takes place not only in the salivary glands, this could be responsible for the elevated serum levels of sICAM-1. Additionally, sICAM-1 has been proposed as a potential therapeutic target [18]. As nSS syndrome occurs when the lacrimal or salivary glands are damaged but it is not caused by an autoimmune disorder, in nSS patients, sICAM-1 serum levels were not elevated and remained at control group level.

Chemokine RANTES is chemotactic for T cells, eosinophils, and basophils. It plays an important role in recruiting leukocytes into inflammatory sites. Global transcription analyses have indicated that CCL5 transcripts were upregulated in the salivary glands of C57BL/6.NOD-*Aec1Aec2* mice at the time of the SS onset, correlating with dendritic cells, T cells, and B cells infiltrations [19]. It is known that the concentrations of RANTES increases in the tears of SS patients and correlates with various tear film and ocular surface parameters [20]. In our study, RANTES serum levels were significantly elevated in pSS, sSS, and nSS patients to compare with healthy controls. Other studies dealing with RANTES serum concentrations in SS are very contravenous. There are reports that RANTES serum levels in SS patients are decreased [21], increased [22], or no differences to compare with controls observed [23, 24].

In this study, levels of TFF3 were significantly increased in pSS and sSS patients compared with healthy controls, but no difference was seen between the SS and nSS groups. It is

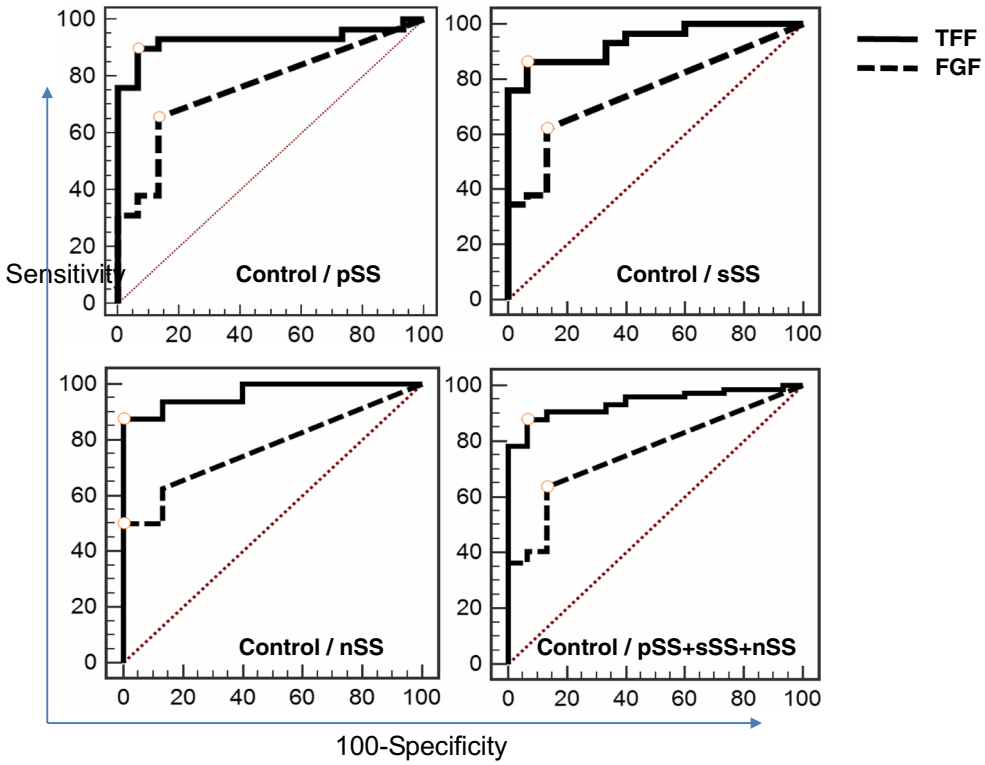

Fig. 2 Comparison of the ROC curves of TFF and FGF. Marked point corresponding Youden index. ROC curves for pSS, sSS, and nSS patients and all patients together (pSS + sSS + nSS) are plotted

known that TFF3 performs a broad variety of protective functions on surface of epithelium. The TFF peptides are mucus-associated and show a tissue-specific expression pattern. Its main function is in enhancing wound healing by promoting tissue restitution. Once the integrity of the epithelial layer is impaired by a defect or an injury, cells of the surrounding unaffected tissue migrate into the affected area and ensure re-epithelialization process [25]. TFF3 is also present in human salivary gland. It was shown that inflammatory factors or ocular surface damage, as they occur in dry eye disease, lead to an increase of TFF3 tear film concentration [26]. TFF3 is a promising therapeutic agent for ocular surface defects and especially for dry eye syndrome [27].

Adiponectin is one of the adipocytokines secreted from visceral adipose tissue and is the only secreted by mature adipocytes. Studies have reported that the levels of adiponectin are elevated in autoimmune diseases, including SS [28, 29]. Adiponectin is mainly released by adipose tissue, but it can be secreted by salivary gland cells. Salivary adiponectin was proposed as a potential biomarker of SS [30]. In our study, concentrations of adiponectin in all studied groups were at a similar level. It is known that adiponectin serum concentrations correlate with insulin sensitivity, type 2 diabetes, severity of obesity, and cardiovascular diseases [28, 31–33]. We hypothesize that in our study groups the volunteers may had other disorders, which interfered with our

Table 3 Data obtained from analysis of ROC curves of TFF and FGF

Protein	Patients	AUC	SE	*P*	*J*	Cutoff value	Sensitivity	Specificity	PPV	NPV
TFF	pSS	0.929	0.0422	< 0.0001	0.8299	> 20.7 ng/ml	89.66	93.33	59.99	98.8
	sSS	0.94	0.032	< 0.0001	0.8043	> 20.7 ng/ml	87.1	93.33	59.2	98.5
	nSS	0.965	0.0285	< 0.0001	0.875	> 24.3 ng/ml	87.5	100	100	98.6
FGF	pSS	0.763	0.0638	< 0.0001	0.5218	> 0 pg/ml	65.52	86.67	35.3	95.8
	sSS	0.751	0.0628	0.0001	0.4874	> 0 pg/ml	62.07	86.67	34.1	95.4
	nSS	0.771	0.074	0.0003	0.5	> 13.0 pg/ml	50	100	100	94.7

AUC, area under the ROC curve; *SE*, standard error; *P*, significance level; *J*, Youden index (the maximum vertical distance between the ROC curve and the diagonal line); *PPV*, positive predictive value (probability that the disease is present when the test is positive); *NPV*, negative predictive value (probability that the disease is not present when the test is negative). Cutoff value, Sensitivity, Specificity, PPV, and NPV were estimated at the point of Youden index. Difference between areas/significance level: pSS, TFF/FGF 0.167/$p = 0.0032$; sSS, TFF/FGF 0.185/$p = 0.0143$; nSS, TFF/FGF 0.205/$p = 0.0077$

obtained results. The data were not analysed and grouped according to other diseases.

FGF are heparin-binding protein crucial to embryogenesis, angiogenesis, and wound healing. It is expressed widely during normal embryonic development and often in adult tissues at sites of injury, where it contributes to wound healing [34]. There are not many studies dealing with SS and FGF. Szodoray et al. performed microarrays to measure serum cytokine levels of patients with pSS and healthy individuals [35]. In that study, no significant difference was observed in FGF levels between pSS and controls. Our results may contrast with previous study and due to differences in study cohort (aforementioned study population consisted only of nine patients and nine controls).

In conclusion, levels of FGF, TFF3, and RANTES were significantly increased in pSS, sSS, and nSS patients with compared healthy controls but no difference was seen between the SS and nSS groups. sICAM-1 was significantly elevated in pSS and sSS patients compared with the nSS group. Clinical manifestations of SS range from autoimmune exocrinopathy to extraglandular (systemic) involvement which lead to late diagnosis. So, among selected molecules, sICAM-1 might be useful as an additional parameter for differential diagnosis of SS and nSS. Based on the ROC analysis, serum TFF has a better predictive value for SS than FGF.

However, further replication of studies with a larger number of subjects is necessary to validate our results.

Compliance with ethical standards

This study was approved by the Vilnius Regional Biomedical Research Ethics Committee (2014-05-20, No. 158200-14-733-248), and written consent was obtained from each participant.

Disclosures None.

References

1. Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, Daniels TE, Fox PC, Fox RI, Kassan SS, Pillemer SR, Talal N, Weisman MH, European Study Group on Classification Criteria for Sjögren's Syndrome (2002) Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 61:554–558
2. Brito-Zerón P, Baldini C, Bootsma H, Bowman SJ, Jonsson R, Mariette X, Sivils K, Theander E, Tzioufas A, Ramos-Casals M (2016) Sjögren's syndrome. Nat Rev Dis Primers 2. https://doi.org/10.1038/nrdp.2016.47
3. Champey J, Corruble E, Gottenberg JE, Buhl C, Meyer T, Caudmont C, Bergé E, Pellet J, Hardy P, Mariette X (2006) Quality of life and psychological status in patients with primary Sjögren's syndrome and sicca symptoms without autoimmune features. Arthritis Rheum 55:451–457
4. Rosenquist R (2008) Introduction: the role of inflammation, autoimmune disease and infectious agents in development of leukaemia and lymphoma. J Intern Med 264:512–513
5. Griffiths I, Kelly C (1993) Systemic features. In: Venables PJW (ed) Sjögren's syndrome: an advisory guide for patients and doctors. Manor House Marketing, London
6. Scofield RH, Asfa S, Obeso D, Jonsson R, Kurien BT (2005) Immunization with short peptides from the 60-kDa Ro antigen recapitulates the serological and pathological findings as well as the salivary gland dysfunction of Sjögren's syndrome. J Immunol 175: 8409–8414
7. Stefanski AL, Tomiak C, Pleyer U, Dietrich T, Burmester GR, Dörner T (2017) The diagnosis and treatment of Sjögren's syndrome. Dtsch Arztebl Int 26:354–361. https://doi.org/10.3238/arztebl.2017.0354
8. Ramos-Casals M, Solans R, Rosas J, Camps MT, Gil A, del Pino-Montes J, Calvo-Alen J, Jiménez-Alonso J, Micó ML, Beltrán J, Belenguer R, Pallarés L, GEMESS Study Group (2008) GEMESS Study Group: primary Sjögren syndrome in Spain: clinical and immunologic expression in 1010 patients. Medicine 87:210–219
9. Haneji N, Nakamura T, Takio K, Yanagi K, Higashiyama H, Saito I, Noji S, Sugino H, Hayashi Y (1997) Identification of α-fodrin as a candidate autoantigen in primary Sjögren's syndrome. Science 276: 604–607
10. Ruffatti A, Ostuni P, Grypiotis P, Botsios C, Tonello M, Grava C, Favaro M, Todesco S (2004) Sensitivity and specificity for primary Sjögren's syndrome of IgA and IgG anti-α-fodrin antibodies detected by ELISA. J Rheumatol 31:504–507
11. Zandbelt MM, Vogelzangs J, Van De Putte LB et al (2004) Anti-α-fodrin antibodies do not add much to the diagnosis of Sjögren's syndrome. Arthritis Res Ther 6:33–38
12. Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM, Rasmussen A, Scofield H, Vitali C, Bowman SJ, Mariette X, the International Sjögren's Syndrome Criteria Working Group (2017) 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome: a consensus and data-driven methodology involving three international patient cohorts. Arthritis Rheumatol 69:35–45
13. Neogi T, Aletaha D, Silman AJ et al (2010) The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis: phase 2 methodological report. Arthritis Rheum 62:2582–2591
14. Deeths MJ, Mescher MF (1999) ICAM-1 and B7-1 provide similar but distinct costimulation for CD8+ T cells, while CD4+ T cells are poorly costimulated by ICAM-1. Eur J Immunol 29:45–53
15. Chen WS, Lin KC, Chen CH et al (2009) Autoantibody and biopsy grading are associated with expression of ICAM-1, MMP-3, and TRAIL in salivary gland mononuclear cells of Chinese patients with Sjogren's syndrome. J Rheumatol 36:989–996
16. Turkcapar N, Sak SD, Saatci M, Duman M, Olmez U (2005) Vasculitis and expression of vascular cell adhesion molecule-1, intercellular adhesion molecule-1, and E-selectin in salivary glands of patients with Sjogren's syndrome. J Rheumatol 32:1063–1070
17. Błochowiak K, Olewicz-Gawlik A, Trzybulska D et al (2017) Serum ICAM-1, VCAM-1 and E-selectin levels in patients with primary and secondary Sjögren's syndrome. Adv Clin Exp Med 26:835–842
18. Pflugfelder SC, Stern M, Zhang S, Shojaei A (2017) LFA-1/ICAM-1 interaction as a therapeutic target in dry eye disease. J Ocul Pharm Therap 33:5–12. https://doi.org/10.1089/iop.2016.0105
19. Nguyen CQ, Sharma A, Lee BH, She JX, McIndoe RA, Peck AB (2009) Differential gene expression in the salivary gland during development and onset of xerostomia in Sjogren's syndrome-like disease of the C57BL/6.NOD-Aec1Aec2 mouse. Arthritis Res Ther 11:R56

20. Won C, Seung-Hyun L, Kyung-Chul Y (2011) Analysis of CCL5 concentration in tears of dry eye patients. J Korean Ophthalmol Soc 52(6):658–664
21. Moutsopoulos NM, Katsifis GE, Angelov N, Leakan RA, Sankar V, Pillemer S, Wahl SM (2008) Lack of efficacy of etanercept in Sjögren syndrome correlates with failed suppression of tumour necrosis factor α and systemic immune activation. Ann Rheum Dis 67:1437–1443
22. Tzec-Pérez A , Barbosa-Cobos RE , Lugo-Zamudio GE, et al (2016) Cytokine and chemokine levels in serum and saliva as disease activity biomarkers in patients with primary Sjögren's syndrome Mexico Meeting: 2016 ACR/ARHP Annual Meeting Date of 1rst publication: September 28, 2016
23. Olsson P, Skogstrand K, Nilsson A, Turesson C, Jacobsson LTH, Theander E, Houen G, Mandl T (2018) Smoking, disease characteristics and serum cytokine levels in patients with primary Sjögren's syndrome. Rheum Int 38:1503–1510
24. Pollard RPE, Abdulahad WH, Bootsma H, Meiners PM, Spijkervet FKL, Huitema MG, Burgerhof JGM, Vissink A, Kroese FGM (2013) Predominantly pro-inflammatory cytokines decrease after b cell depletion therapy in patients with primary Sjögren's syndrome. Ann Rheum Dis 72:2048–2050. https://doi.org/10.1136/annrheumdis-2013-203447
25. Kjellev S (2008) The trefoil factor family-small peptides with multiple functionalities. Cell Mol Life Sci 66:1350–1369
26. Schulze U, Hampel U, Sel S, Contreras-Ruiz L, Schicht M, Dieckow J, Diebold Y, Paulsen F (2014) Trefoil factor family peptide 3 (TFF3) is upregulated under experimental conditions similar to dry eye disease and supports corneal wound healing effects in vitro. Invest Ophthalmol Vis Sci 55:3037–3042
27. Paulsen F, Berry M (2006) Mucins and TFF peptides of the tear film and lacrimal apparatus. Prog Histochem Cytochem 41:1–53
28. Yildiz Y, Ozaksit G, Serdar Unlu B, Ozgu E, Energin H, Kaba M, Ugur M (2013) Serum adiponectin level and clinical, metabolic, and hormonal markers in patients with polycystic ovary syndrome. Int J Fertil Steril 7(4):331–336
29. Toussirot E, Gaugler B, Bouhaddi M, Nguyen NU, Saas P, Dumoulin G (2010) Elevated adiponectin serum levels in women with systemic autoimmune diseases. Med Infl 2010:1–6. https://doi.org/10.1155/2010/938408
30. Tvarijonaviciute A, Zamora C, Martinez-Subiela S, Tecles F, Pina F, Lopez-Jornet P (2018) Salivary adiponectin, but not adenosine deaminase, correlates with clinical signs in women with Sjögren's syndrome: a pilot study. Clin Oral Invest 23:1407–1414. https://doi.org/10.1007/s00784-018-2570-3
31. Pajvani UB, Hawkins M, Combs TP, Rajala MW, Doebber T, Berger JP, Wagner JA, Wu M, Knopps A, Xiang AH, Utzschneider KM, Kahn SE, Olefsky JM, Buchanan TA, Scherer PE (2004) Complex distribution, not absolute amount of adiponectin, correlates with thiazolidinedione-mediated improvement in insulin sensitivity. J Biol Chem 279(13):12152–12162
32. Nakashima R, Kamei N, Yamane K, Nakanishi S, Nakashima A, Kohno N (2006) Decreased total and high molecular weight adiponectin are independent risk factors for the development of type 2 diabetes in Japanese-Americans. J Clin Endocrinol Metab 91(10):3873–3877
33. Yamauchi T, Kamon J, Ito Y, Tsuchida A, Yokomizo T, Kita S, Sugiyama T, Miyagishi M, Hara K, Tsunoda M, Murakami K, Ohteki T, Uchida S, Takekawa S, Waki H, Tsuno NH, Shibata Y, Terauchi Y, Froguel P, Tobe K, Koyasu S, Taira K, Kitamura T, Shimizu T, Nagai R, Kadowaki T (2003) Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. Nature 423(6941):762–769
34. Basilico C, Moscatelli D (1992) The FGF family of growth factors and oncogenes. Adv Cancer Res 59:115
35. Szodoray P, Alexy P, Brun JG et al (2004) Circulating cytokines in primary Sjögren's syndrome determined by a multiplex cytokine Array system. Scand J Immunol 59:592–599