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ABSTRACT

Objective. *The majority of women with primary Sjögren's syndrome (pSS) suffer from vaginal dryness, which negatively impacts daily and sexual activities. As little is known about the aetiology and clinical context of this complaint, this study investigated the relationship between vaginal dryness and other clinical parameters associated with pSS.*

Methods. *Female participants of the REgistry of Sjögren syndrome at UMCG – LongiTudinal (RESULT) cohort who fulfilled ACR-EULAR and/or AECG classification criteria for pSS were included, using baseline data for analyses. Patient-reported vaginal dryness (range 0–10) was correlated with demographic characteristics, systemic disease activity (i.e. ESSDAI), Sjögren's Syndrome Disease Damage Index, salivary and lacrimal gland function, patient-reported outcomes (ESSPRI, MFI), serology and quality of life (SF-36, EQ-5D). Significantly associated parameters ($p<0.05$) were corrected for potential confounders.*

Results. *This cross-sectional study included 199 women with pSS; mean age was 52±14 years, 53% were postmenopausal, and median vaginal dryness score was 5 (IQR 2-7). Vaginal dryness was significantly associated with older age, postmenopausal status, peripheral neuropathy, oral and ocular dryness, ESSPRI and SF-36 mental and general health. After correction for age, menopausal status and medication use, peripheral neuropathy (B=1.632), oral dryness (B=0.302), and ocular dryness (B=0.230) were independently associated with vaginal dryness.*

Conclusion. *The independent association of vaginal dryness with oral and ocular dryness might imply that the aetiology of these symptoms is partly shared. Of all extraglandular features, only peripheral neuropathy was independently associated with vaginal dryness, suggesting that peripheral neuropathy plays a significant role in the pathology of vaginal dryness in pSS.*

Introduction

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease that predominantly affects the salivary and lacrimal glands, resulting in oral and ocular dryness complaints characteristic of the disease (1-2). Extraglandular manifestations such as fatigue, Raynaud's phenomenon, vasculitis, and neurological involvement can also occur in patients with pSS (1-3). In addition to the well-described oral and ocular sicca symptoms, vaginal dryness and dyspareunia are common in women with pSS (4, 5). Of female pSS patients, 68% reported a change in sexual function, for which vaginal dryness was identified as one of the main causes (4). The impaired sexual function is reflected by lower scores in the Female Sexual Function Index (FSFI) domains arousal, desire, lubrication, orgasm and pain (5, 7, 8).

Despite the significant impact on daily life, the aetiology of vaginal dryness remains unclear. Since pSS primarily affects the exocrine glands, dysfunction of exocrine glands in the female genital tract has been considered as a possible cause of vaginal dryness. However, no exocrine glands are present inside the vagina, and the vestibular glands (Bartholin's glands) only play a minor role in lubrication (9, 10). Vaginal lubrication during sexual arousal is mainly induced by dilation of blood vessels in the vaginal wall and subsequent formation of a transudate. Mucus production by the endocervical epithelium also contributes to lubrication. Previous research showed peri-epithelial lymphocytic infiltration of the vaginal mucosa

of pSS patients, suggesting that local inflammation of the vaginal mucosa might contribute to vaginal dryness (4, 11). Our recent study extended these findings by additionally showing a decrease in vascular smooth muscle cells in the vaginal wall, pointing towards vascular dysfunction (12). The possible dysfunction of these vessels, potentially due to local inflammation, could contribute to vaginal dryness to a significant extent.

To gain more insight into the aetiology, clinical context, and impact of vaginal dryness in pSS, this study aimed to identify clinical parameters which are associated with vaginal dryness in women with pSS.

Methods

Patient inclusion

In this cross-sectional study, women with pSS who participated in the Registry of Sjögren Syndrome at UMCG – LongiTudinal (RESULT) cohort were included (13). The RESULT cohort is an ongoing prospective observational cohort study, which includes consecutive patients with probable or confirmed pSS who visited the outpatient clinic of the department of Rheumatology and Clinical Immunology of the University Medical Center Groningen (UMCG) since January 2016. Inclusion criteria for the present study were a completed baseline visit before October 2020 and fulfilment of the 2016 American College of Rheumatology (ACR)-European League Against Rheumatism (EULAR) and/or 2002 American-European Consensus Group (AECG) classification criteria for pSS (14, 15). Exclusion criteria were male gender and missing data on vaginal dryness at baseline.

All data were obtained within the RESULT cohort, which was approved by the Medical Ethics Committee of the UMCG (METC 2014/491) and was conducted according to the declaration of Helsinki. All included participants provided written informed consent.

Data collection

For this study, baseline data were used for analyses. Demographic characteristics were age, sex, smoking and menopausal status. Clinical assessments included blood pressure, EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI), physician-reported global disease activity (GDA), ocular staining score (OSS), Schirmer's test and unstimulated (UWSF) and stimulated whole salivary flow (SWSF). Disease damage was assessed with the total score of the Sjögren's Syndrome Disease Damage Index (SSDDI), as well as the following SSDDI domain scores: neurological damage, pleuropulmonary damage, renal impairment and lymphoproliferative disease. Biological parameters used for this study were: anti-SSA/-SSB antibody status, serum levels of rheumatoid factor, total IgG, and cryoglobulins.

Participants completed questionnaires about ocular, oral and vaginal dryness (assessed with numeric rating scale (NRS) of 0–10), EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI), and Multidimensional Fatigue Inventory (MFI).

The impact of vaginal dryness on health-related quality of life (QoL) was assessed using the EuroQoL five dimensions health status (EQ-5D-5L), and the 36-item Short Form health survey (SF-36) which includes eight domains: physical functioning, social functioning, role limitations due to physical problems, role limitations due to emotional problems, mental health, vitality, bodily pain, and general health.

Statistical analyses

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 23.0. Results were expressed as number (%) of patients for categorical data and mean ± SD or median (IQR) for normally and non-normally distributed continuous data, respectively. First, the univariable relationship between vaginal dryness and demographic and clinical parameters (*e.g.* age, menopausal status, disease activity, damage, gland function, patient-reported outcome and serology) was explored. Mann-Whitney U-test was used to compare vaginal dryness scores between groups with and without certain demographic characteristics or disease features. Spearman correlation coefficient (ϱ) was used to correlate vaginal dryness scores with other continuous variables and interpreted as poor (0.0–0.2), fair (0.2–0.4), moderate (0.4–0.6), good (0.6–0.8) or strong association (0.8–1.0) (16). Clinical parameters with a significant association with vaginal dryness were then corrected for potential confounders with a multivariable model. Parameters that remained significant after correcting for confounders were included in a multivariable linear regression model with vaginal dryness score as dependent variable. This model consisted of a block of confounders (entered using the Enter method) and a block with disease features (entered using the Forward selection method). Furthermore, the relationship between vaginal dryness and QoL was explored using Spearman correlation coefficient. *p*-values <0.05 were considered statistically significant.

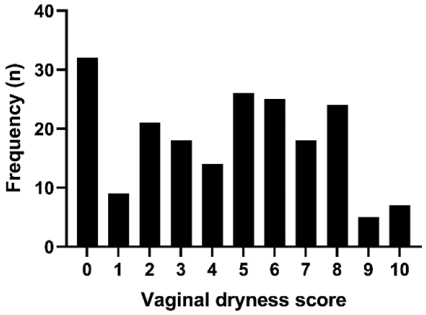

Fig. 1. Distribution of the numeric rating scale vaginal dryness scores within the cohort.

Results

Patient characteristics

In October 2020, the RESULT database contained baseline data of 245 pSS patients who fulfilled ACR-EULAR and/or AECG criteria. Twenty-nine patients were excluded from the current study because of male gender and 17 patients because of missing data on vaginal dryness at baseline. Baseline data of the remaining 199 women of the RESULT cohort were used for this study. The mean age of the study population was 52±14 years and median disease duration was 8 years (IQR 5-14). 35.2% of the patients were premenopausal, 10.1% perimenopausal and 53.3% postmenopausal (1.4% missing data). The median ESSDAI score was

Table I. Baseline characteristics of the study cohort.

Characteristics	Study population (n=199)
Demographic characteristics	
Age (years)	52 ± 14
Disease duration since diagnosis (years)	10 ± 7
Mean arterial pressure (MAP)	94.8 ± 11.2
Menopausal status	
Premenopausal	70 (35.2)
Perimenopausal	20 (10.1)
Postmenopausal	106 (53.3)
Clinical outcomes	
ESSDAI total score (range 0-123)	4.0 (2.0 - 7.0)
Physician GDA (range 0-10)	2.0 (1.0 - 3.0)
SSDDI total score	2.0 (1.0 - 3.0)
UWSF (ml/min)	0.04 (0.01 - 0.13)
SWSF (ml/min)	0.43 (0.11 - 0.84)
Schirmer (mean of both eyes)	3.8 (1.0 – 10.0)
Ocular staining score (mean of both eyes)	2.0 (0.5 - 4.0)
Biological parameters	
Rheumatoid factor (IU/ml)	17.0 (2.9 - 45.5)
IgG (g/l)	15.4 (11.2 - 19.9)
Anti-SSA positive	172 (86.4)
Anti-SSB positive	108 (54.3)
Cryoglobulins positive	56 (26.4)
Questionnaires	
ESSPRI total score (range 0-10)	6.3 (4.7 - 7.2)
dryness (range 0-10)	7.0 (5.0 - 8.0)
fatigue (range 0-10)	7.0 (5.0 - 7.0)
pain (range 0-10)	5.0 (3.0 - 7.0)
Vaginal dryness (range 0-10)	5.0 (2.0 - 7.0)
Ocular dryness (range 0-10)	7.0 (5.0 - 8.0)
Oral dryness (range 0-10)	7.0 (5.0 - 8.0)
Patient GDA (range 0-10)	7.0 (4.0 - 8.0)
MFI physical fatigue (range 4-20)	14.0 (10.0 - 17.0)
MFI mental fatigue (range 4-20)	12.0 (7.0 - 14.0)
Quality of life	
SF-36	
Physical functioning	70.0 (55.0 - 90.0)
Social functioning	62.5 (50.0 - 87.5)
Role limitations (physical problems)	50.0 (31.3 - 68.8)
Role limitations (emotional problems)	75.0 (50.0 - 100.0)
Mental health	75.0 (60.0 - 85.0)
Vitality	50.0 (31.3 - 62.5)
Pain	67.4 (44.9 - 77.6)
General health	40.0 (25.0 - 50.0)
EQ-5D-5L	0.83 (0.75 - 0.89)

Data are presented as mean±SD, n (%) or median (IQR).
ESSDAI: EULAR Sjögren's syndrome disease activity index; GDA: general disease activity; SSDDI: Sjögren's syndrome disease damage index; UWSF: unstimulated whole salivary flow; SWSF: stimulated whole salivary flow; ESSPRI: EULAR Sjogren's syndrome patient reported index; NRS: numeric rating scale; MFI: multidimensional fatigue inventory.

4 (IQR 2-7), median ESSPRI score was 6.3 (IQR 4.7-7.2), and median vaginal dryness NRS was 5 (IQR 2-7). Figure 1 shows the distribution of vaginal dryness scores within the cohort. All demographic and clinical characteristics of the study population are summarised in Table I.

Associations between vaginal dryness and clinical parameters

Univariable analyses showed significant positive correlations of vaginal dryness with age (ϱ=0.18), ESSPRI (ϱ=0.22), oral dryness (ϱ=0.37), ocular dryness (ϱ=0.29) and patient GDA (ϱ=0.15). A significant inverse correlation with UWSF (ϱ=-0.17) was observed. Other clinical parameters, including ESSDAI, patient-reported fatigue, and biological parameters were not significantly correlated with vaginal dryness (Table II).

Univariable group comparisons showed significantly higher vaginal dryness scores in pSS patients with long-lasting and stable peripheral neuropathy (as defined by the SSDDI) compared to patients without neuropathy (median 7, IQR 5.0–8.5 *vs*. 5, IQR 2.0–6.0, p=0.003) (Table III). Of the 16 patients with long-lasting and stable peripheral neuropathy, the type of neuropathy was defined by electromyography (EMG) in nine cases: three patients had sensory neuropathy, two had sensorimotor neuropathy, two had small fibre neuropathy, one had axonal neuropathy and one had peroneal neuropathy. Of the remaining seven patients, EMG data on the type of neuropathy was lacking as diagnosis was made on clinical ground.

Vaginal dryness scores were also significantly higher in pSS patients with hypertension compared to patients without hypertension (median 6, IQR 4.0–8.0 *vs*. 4, IQR 2.0–6.5, p=0.036), and in postmenopausal pSS patients compared to premenopausal patients (median 5, IQR 3.0–7.0 *vs*. 4, IQR 1.0-6.0, p=0.015). No significant difference in symptoms of vaginal dryness were found when comparing groups based on other disease features (Table III).

All of the parameters which were univariably associated with vaginal dryness, except UWSF and hypertension, remained significantly associated with vaginal dryness after correcting for potential confounders. These confounders included age, menopausal status, use of a biologic DMARD (rituximab up to a year before inclusion, abatacept up to six months before inclusion) and use of medication with vaginal dryness as potential side-effect (calcium channel blockers, beta blockers, angiotensin-converting enzyme inhibitors and selective serotonin reuptake inhibitors). Biologic DMARD use was included as confounder, because previous trials showed that these drugs may to some extent improve symptoms of

Table II. Correlations between vaginal dryness scores and continuous parameters.

Variable	n included	rho	*p*-value
Demographic characteristics			
Age (years)	199	0.181	**0.011**
Clinical outcomes			
Mean arterial pressure (MAP)	196	0.039	0.588
ESSDAI total score (range 0-123)	192	-0.082	0.259
cutaneous domain	193	-0.080	0.270
respiratory domain	193	-0.045	0.536
articular domain	193	0.024	0.735
muscular domain	193	0.095	0.188
peripheral nervous system domain	193	0.047	0.516
haematological domain	193	-0.058	0.419
glandular domain	193	-0.008	0.907
constitutional domain	194	-0.088	0.222
lymphadenopathy domain	193	-0.134	0.063
biological domain	192	-0.030	0.675
Physician GDA (range 0-10)	172	0.009	0.904
SSDDI total score	162	0.067	0.397
UWSF (ml/min)	182	-0.167	**0.024**
SWSF (ml/min)	182	-0.063	0.401
Schirmer (mean of both eyes)	186	-0.121	0.101
Ocular staining score (mean of both eyes)	188	0.063	0.388
Tender points (range 0-18)	186	0.096	0.191
Biological parameters			
Rheumatoid factor (IU/ml)	195	0.064	0.371
IgG (g/l)	195	0.011	0.884
Questionnaires			
ESSPRI total score (range 0-10)	199	0.220	**0.002**
dryness (range 0-10)	199	0.348	**<0.001**
fatigue (range 0-10)	199	0.120	0.091
pain (range 0-10)	199	0.105	0.141
Oral dryness (range 0-10)	199	0.293	**<0.001**
Ocular dryness (range 0-10)	199	0.367	**<0.001**
Patient GDA (range 0-10)	199	0.145	**0.041**
MFI physical fatigue (range 4-20)	199	0.104	0.143
MFI mental fatigue (range 4-20)	199	0.136	0.055
Quality of life			
SF-36			
Physical functioning	199	-0.113	0.111
Social functioning	199	-0.142	**0.046**
Role limitations (physical problems)	199	-0.081	0.255
Role limitations (emotional problems)	199	-0.180	**0.011**
Mental health	199	-0.084	0.237
Vitality	199	-0.081	0.255
Pain	199	-0.098	0.166
General health	199	-0.182	**0.010**
EQ-5D-5L	199	-0.136	0.083

Significant *p*-values are presented in bold.
ESSDAI: EULAR Sjögren's syndrome disease activity index; SSDDI: Sjögren's syndrome disease damage index; ESSPRI: EULAR Sjögren's syndrome patient reported index; GDA: general disease activity; NRS: numeric rating scale; MFI: mental fatigue index.

dryness and/or sexual function (17, 18).

In the multivariable analysis, which included all potential predictors of vaginal dryness as well as potential confounders, long-lasting peripheral neuropathy (B=1.63), oral dryness (B=0.30), and ocular dryness (B=0.23) were independently associated with vaginal dryness (Fig. 2A-C, Table IV).

Vaginal dryness in relation to quality of life

Vaginal dryness showed significant inverse correlations with the SF-36 domains social functioning (ϱ=-0.14), role limitations due to emotional problems (ϱ=-0.18) and general health (ϱ=-0.18) (Fig. 2D-F, Table II). The observed correlations were also significant when corrected for potential confounders (data not shown). Vaginal dryness showed no significant correlations with the EQ-5D-5L and the other SF-36 domains (Table II).

Discussion

To gain more insight into the aetiology and clinical context of vaginal dryness in pSS, this study aimed to identify clinical parameters that are associated with vaginal dryness in women with pSS. We showed that in pSS patients, symptoms of oral and ocular dryness and long-lasting and stable peripheral neuropathy according to the SSDDI were independently associated with vaginal dryness, also after correction for potential confounders (age, postmenopausal status and medication use).

The finding that oral and ocular dryness showed a fair to moderate correlation with vaginal dryness indicates that more severe vaginal dryness often occurs together with more severe sicca complaints of eyes and/or mouth. The observed correlation suggests that a partly shared pathophysiological mechanism underlies oral, ocular and vaginal dryness. Oral and ocular dryness are generally considered to result from dysfunction of the salivary and lacrimal glands (19). In contrast, vaginal lubrication is achieved by a watery transudate which is produced by blood vessels in the vaginal wall, particularly in the aroused state, and by mucous secretions from the endocervical epithelium. Therefore, dysfunction of local exocrine glands is not a probable cause of vaginal dryness in pSS.

Interestingly, we found in our study that vaginal dryness in pSS patients is associated with peripheral neuropathy. The peripheral nervous system indeed plays an important role in vaginal lubrication by regulating blood flow in the vaginal wall (9, 10). In a state of arousal, the central nervous system is activated and stimulates the peripheral nerves in the vaginal wall to secrete neuropeptides, such as nitric oxygen (NO) and vasoactive intestinal peptide (VIP) (9, 10). These neuropeptides cause a vasodilation of the vessels in the vaginal wall, allowing for an increased vaginal blood flow and genital vasocongestion. Due to the vasocongestion, the vaginal wall

Table III. Comparison of vaginal dryness scores between groups.

Variable	Present n	Absent n	Present median (IQR)	Absent median (IQR)	*p*-value
Demographic characteristics					
Postmenopausal status*	106	70	5.0 (3.0 - 7.0)	4.0 (1.0 - 6.0)	**0.015**
Clinical outcomes					
Cardiovascular disease	23	176	4.0 (2.0 - 6.5)	5.0 (2.0 - 7.0)	0.761
Hypertension	28	171	6.0 (4.0 - 8.0)	4.0 (2.0 - 6.5)	**0.036**
Thyroid disease	21	178	6.0 (2.0 - 8.0)	5.0 (2.0 - 7.0)	0.101
Diabetes	5	194	6.0 (3.0 - 7.0)	5.0 (2.0 - 7.0)	0.812
SSDDI Neurological damage	16	179	7.0 (5.0 - 8.5)	5.0 (2.0 - 6.0)	**0.003**
Long-lasting stable peripheral neuropathy**	16	179	7.0 (5.0 - 8.5)	5.0 (2.0 - 6.0)	**0.003**
SSDDI Pleuropulmonary damage	9	186	3.0 (0.0 - 6.0)	5.0 (2.0 - 7.0)	0.188
Interstitial fibrosis	5	190	4.0 (3.0 - 6.0)	5.0 (2.0 - 7.0)	0.777
Bronchiectasis	3	192	6.0 (4.0 - 6.5)	5.0 (2.0 - 7.0)	0.693
Significant irreversible functional damage	3	192	0.0 (0.0 - 3.5)	5.0 (2.0 - 7.0)	0.256
SSDDI Renal impairment	4	190	3.5 (2.5 - 6.0)	5.0 (2.0 - 7.0)	0.906
Long-lasting and stable increased serum creatinine or reduced GFR	3	191	3.0 (2.5 - 5.5)	5.0 (2.0 - 7.0)	0.996
Tubular acidosis***	2	192	3.0 (2.0 - 4.0)	5.0 (2.0 - 7.0)	0.480
SSDDI Lymphoproliferative disease	28	167	4.0 (1.5 - 7.0)	5.0 (2.0 - 7.0)	0.935
B cell MALT lymphoma****	28	167	4.0 (1.5 - 7.0)	5.0 (2.0 - 7.0)	0.935
Biological parameters					
SSA antibodies	172	16	5.0 (2.0 - 7.0)	5.0 (1.0 - 6.0)	0.536
SSB antibodies	108	81	4.0 (2.0 - 6.0)	5.0 (2.0 - 7.0)	0.307
Cryoglobulins	55	136	4.0 (2.5 - 6.0)	5.0 (2.0 - 7.0)	0.771

*For postmenopausal status: absent = premenopausal.
**Long-lasting and stable peripheral neuropathy has the same values as neurological damage, because the other feature of this domain, long-lasting and stable central nerve system involvement, did not occur in any of the patients.
***Urinary pH>6 and serum bicarbonate <15 mmol/l in 2 consecutive tests.
****B cell MALT lymphoma has the same values as lymphoproliferative disease, because the other features of this domain, other B cell lymphomas, multiple myeloma and Waldenströms macroglobulinemia, did not occur in any of the patients.
SSDDI: Sjögren's syndrome disease damage index; GFR: glomerular filtration rate.

Table IV. Multivariable regression model of the association between vaginal dryness and clinical parameters.

	B	CI	*p*-value
Oral dryness (range 0-10)	0.302	0.095-0.509	0.004
SSDDI Long-lasting and stable peripheral neuropathy (present vs. absent)	1.632	0.159-3.105	0.030
Ocular dryness (range 0-10)	0.230	0.016-0.444	0.035

Results were obtained with a multivariable linear regression model. Variables included were in block 1 (enter method): age (confounder), postmenopausal status (confounder), use of medication with side effect vaginal dryness (confounder) and in block 2 (forward selection method) SSDDI long-lasting and stable peripheral neuropathy, ESSPRI, NRS ocular dryness, NRS oral dryness and patient-reported GDA. Table shows the final model.
NRS: numeric rating scale; SSDDI: Sjögren's syndrome disease damage index; ESSPRI: EULAR Sjögren's syndrome patient reported index; GDA: general disease activity.

thickens and the pressure inside the vaginal vessels rises. The increase in blood flow and pressure causes an increase in the production of transudate. If the peripheral nervous system is dysfunctional, as is the case in a noticeable number of pSS patients, vasodilatation might not occur properly, possibly leading to insufficient lubrication (9, 10). Previous literature reports that neurological manifestations can occur in 5–45% of pSS patients. This wide range is likely due to varying definitions and diagnostic measures. Of these manifestations, peripheral neuropathy is seen most frequently. Other possible manifestations are central nervous system and autonomous nervous system neuropathies (20, 21). In our cohort, 16 patients showed stable and long-lasting peripheral neuropathy of various subtypes and these patients reported a higher severity of vaginal dryness. Because of the limited number of cases, we could not perform sub-analyses for the different types of peripheral neuropathy.

Van Nimwegen *et al*. (12) showed that in vaginal biopsies of pSS patients, in addition to peri-epithelial lymphocytic infiltrations, the number of smooth muscle cells in the connective tissue was decreased. Whether this decrease is directly or indirectly related to the inflammatory infiltrate and/or to defective innervation is not known. Interestingly, a decrease in VIP immunoreactive nerves was seen in labial salivary glands of SS patients, which may contribute to reduced saliva production (22). A more recent study in a mouse model of SS showed that decreased VIP levels in the salivary glands occurred at a similar age as the onset of salivary secretion loss, and VIP levels gradually decreased as these symptoms progressed (23). Furthermore, treatment with VIP significantly improved exocrine gland function in this mouse model, collectively showing that decreased VIP might be involved in the pathophysiology of saliva production

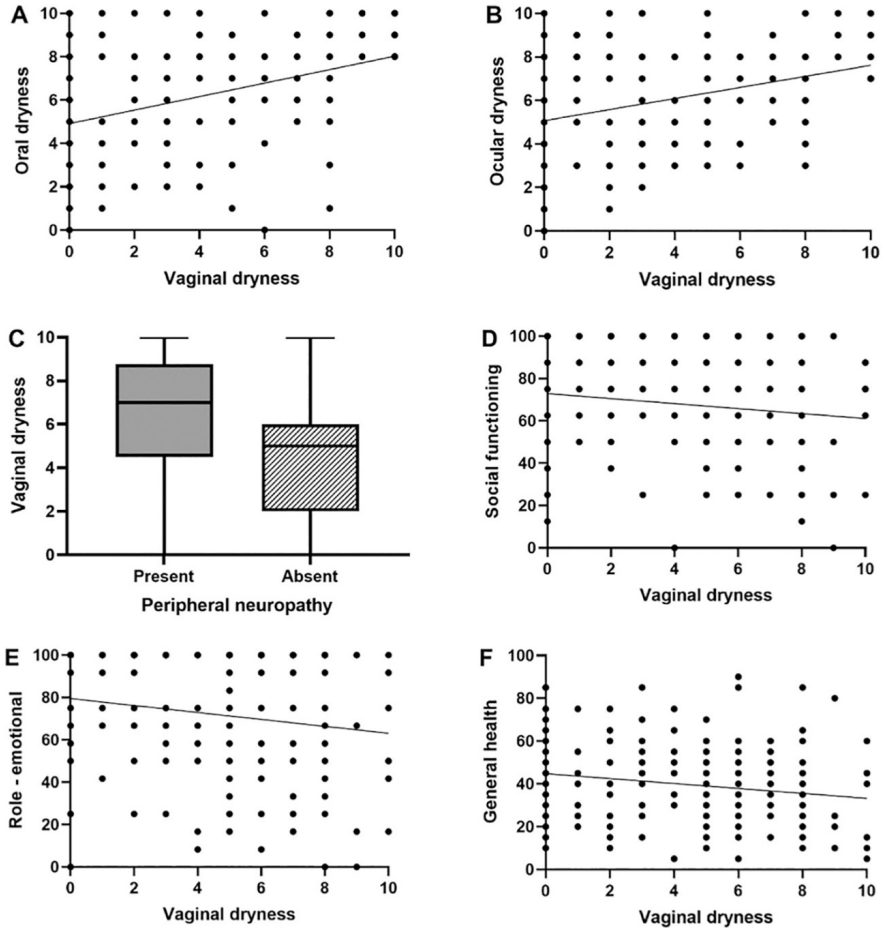

Fig. 2. Scatterplots and boxplot of significant associations between vaginal dryness and oral dryness (**A**), ocular dryness (**B**), peripheral neuropathy (**C**) and SF-36 domains social functioning (D), role limitations due to emotional problems (**E**) and general health (**F**).

in SS (24). Whether decreased VIP and/or NO secretion is responsible for the vaginal dryness in pSS patients remains to be shown. It might be possible that neurological damage and subsequent decrease in VIP secretion is a common pathway in the pathophysiology of oral, ocular as well as vaginal dryness, in addition to the inflammation of the exocrine glands and vaginal wall.

With regard to vaginal dryness, we know that mechanisms of lubrication are different for the non-aroused and aroused state (10). In the non-aroused state, lubrication is achieved by a combination of transudate from the blood vessels in the vaginal wall and mucus from the endocervical epithelium, whereas in the aroused state the vessels in the vaginal wall are largely responsible for the increased lubrication (10). Vaginal dryness in a non-aroused state may therefore have a different pathology than in an aroused state in women with pSS. Peripheral neuropathy might especially be an important factor in the pathology of vaginal dryness in women with pSS in an aroused state, since in the aroused state innervation of blood vessels in the vaginal wall plays an important role.

We also analysed the impact of vaginal dryness on the QoL of women with pSS, using the SF-36 and EQ-5D-5L. General health and domains related to mental components of the SF-36 (social functioning and role limitations due to emotional problems) were significantly and inversely correlated with vaginal dryness. Although correlation coefficients were relatively low, this illustrates the negative impact of vaginal dryness on the mental and general wellbeing of women with pSS. This is in line with other studies that also found negative correlations between vaginal dryness and QoL (4, 6).

There are some limitations to consider regarding this study. First of all, we focused on patient-reported vaginal dryness. To further explore its aetiology, it would be worthwhile to use objective assessments of vaginal lubrication. Another limitation is that we did not distinguish vaginal dryness in a non-aroused state and during arousal. Some disease features were also relatively rare in our patient cohort and therefore group comparisons were limited by the small number of patients. Furthermore, data on anxiety and depression were not available for our cohort, while the presence of these clinical features may modulate disease symptoms and result in a higher symptom burden (25). Depression is also shown to be associated with sexual dysfunction in women with pSS (5). Lastly, this study analysed peripheral neuropathy according to the SSDDI, which is scored when the neuropathy is long-lasting and stable (26). Therefore, patients with recently developed neuropathy or subclinical neuropathy are not scored in the SSDDI and consequently not included in the analysis.

In conclusion, we have shown that vaginal dryness is not only associated with oral and ocular dryness, as might be expected, but also with peripheral neuropathy. Since blood flow is a critical component of lubrication of the vagina, in particular in the aroused state, and since there are some indications that smooth muscle cells in the vaginal wall are affected in pSS patients, we hypothesize that neural innervation of the vaginal blood vessels is affected in pSS patients. Vaginal dryness is a considerable complaint with a negative impact on the quality of life of women with pSS, especially on mental components and general health. Therefore, future studies into the pathophysiological mechanism of this symptom, as well as potential treatment strategies, are warranted.

References

1. BRITO-ZERÓN P, BALDINI C, BOOTSMA H *et al*.: Sjögren syndrome. *Nat Rev Dis Prim* 2016; 2: 16047.
2. STEFANSKI AL, TOMIAK C, PLEYER U, DIETRICH T, BURMESTER GR, DÖRNER T: The Diagnosis and Treatment of Sjögren's Syndrome. *Dtsch Arztebl Int* 2017; 114: 354-61.
3. GARCÍA-CARRASCO M, SISÓ A, RAMOS-CASALS M *et al*.: Raynaud's phenomenon in primary Sjögren's syndrome. Prevalence

and clinical characteristics in a series of 320 patients. *J Rheumatol* 2002; 29: 726-30.
4. MADDALI BONGI S, ORLANDI M, DE MAGNIS A *et al*.: Women with primary sjögren syndrome and with non-Sjögren sicca syndrome show similar vulvar histopathologic and immunohistochemical changes. *Int J Gynecol Pathol* 2016; 35: 585-92.
5. VAN NIMWEGEN JF, ARENDS S, VAN ZUIDEN GS, VISSINK A, KROESE FG, BOOTSMA H: The impact of primary Sjögren's syndrome on female sexual function. *Rheumatology* (Oxford) 2015; 54: 1286-93.
6. MULHERIN DM, SHEERAN TP, KUMARARATNE DS, SPECULAND B, LUESLEY D, SITUNAYAKE RD: Sjögren's syndrome in women presenting with chronic dyspareunia. *Br J Obstet Gynaecol* 1997; 104: 1019-23.
7. PRIORI R, MINNITI A, DERME M *et al*.: Quality of sexual life in women with primary Sjögren syndrome. *J Rheumatol* 2015; 42: 1427-31.
8. ROSEN R, BROWN C, HEIMAN J *et al*.: The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. *J Sex Marital Ther* 2000; 26: 191-208.
9. BERMAN JR: Physiology of female sexual function and dysfunction. *Int J Impot Res* 2005; 17 (Suppl. 1): S44-S51.
10. LEVIN RJ, BOTH S, GEORGIADIS J, KUKKONEN T, PARK K, YANG CC: The physiology of female sexual function and the pathophysiology of female sexual dysfunction (Committee 13A). *J Sex Med* 2016; 13: 733-59.
11. SKOPOULI FN, PAPANIKOLAOU S, MALAMOU-MITSI V, PAPANIKOLAOU N, MOUTSOPOULOS HM: Obstetric and gynaecological profile in patients with primary Sjögren's syndrome. *Ann Rheum Dis* 1994; 53: 569-73.
12. VAN NIMWEGEN JF, VAN DER TUUK K, LIEFERS SC *et al*.: Vaginal dryness in primary Sjögren's syndrome: a histopathological case-control study. *Rheumatology* (Oxford) 2020; 59: 2806-15.
13. MOSSEL E, VAN NIMWEGEN JF, STEL AJ *et al*.: Clinical phenotyping of primary sjögren syndrome patients using salivary gland ultrasonography: data From the RESULT Cohort. *J Rheumatol* 2021; 48: 717-27.
14. SHIBOSKI CH, SHIBOSKI SC, SEROR R *et al*.: 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* 2017; 69: 35-45.
15. VITALI C, BOMBARDIERI S, JONSSON R *et al*.: Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002; 61: 554-8.
16. LANDIS JR, KOCH GG: The measurement of observer agreement for categorical data. *Biometrics* 1977; 33: 159-74.
17. VAN NIMWEGEN JF, MOSSEL E, VAN ZUIDEN GS *et al*.: Abatacept treatment for patients with early active primary Sjögren's syndrome: a single-centre, randomised, double-blind, placebo-controlled, phase 3 trial (ASAP-III study). *Lancet Rheumatol* 2020; 2: E153-63
18. VERSTAPPEN GM, VAN NIMWEGEN JF, VISSINK A, KROESE FGM, BOOTSMA H: The value of rituximab treatment in primary Sjögren's syndrome. *Clin Immunol* 2017; 182: 62-71.
19. RISCHMUELLER M, TIEU J, LESTER S: Primary Sjögren's syndrome. *Best Pract Res Clin Rheumatol* 2016; 30: 189-220.
20. ALUNNO A, CARUBBI F, BARTOLONI E, CIPRIANI P, GIACOMELLI R, GERLI R: The kaleidoscope of neurological manifestations in primary Sjögren's syndrome. *Clin Exp Rheumatol* 2019; 37 (Suppl. 118): S192-8.
21. MEKINIAN A, TENNENBAUM J, LAHUNA C *et al*.: Primary Sjögren's syndrome: central and peripheral nervous system involvements. *Clin Exp Rheumatol* 2020; 38 (Suppl. 126): S103-9.
22. TÖRNWALL J, KONTTINEN YT, HIETANEN J, SORSA T, HUKKANEN M, UUSITALO H: VIP in salivary glands in Sjögren's syndrome. *Br J Rheumatol* 1995; 34: 891-3.
23. HAUK V, CALAFAT M, LAROCCA L *et al*.: Vasoactive intestinal peptide/vasoactive intestinal peptide receptor relative expression in salivary glands as one endogenous modulator of acinar cell apoptosis in a murine model of Sjögren's syndrome. *Clin Exp Immunol* 2011; 166: 309-16.
24. LI C, ZHU F, WU B, WANG Y: Vasoactive intestinal peptide protects salivary glands against structural injury and secretory dysfunction via IL-17A and AQP5 regulation in a model of Sjögren syndrome. *Neuroimmunomodulation* 2017; 24: 300-9.
25. TARN JR, HOWARD-TRIPP N, LENDREM DW *et al*.: Symptom-based stratification of patients with primary Sjögren's syndrome: multidimensional characterisation of international observational cohorts and reanalyses of randomised clinical trials. *Lancet Rheumatol* 2019; 1: e85-e94.
26. VITALI C, PALOMBI G, BALDINI C *et al*.: Sjögren's Syndrome Disease Damage Index and disease activity index: scoring systems for the assessment of disease damage and disease activity in Sjögren's syndrome, derived from an analysis of a cohort of Italian patients. *Arthritis Rheum* 2007; 56: 2223-31.