Review

Discrepancy between subjective symptoms, objective measures and disease activity indexes: the lesson of primary Sjögren's syndrome

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ABSTRACT

Mucosal dryness is a key clinical feature in primary Sjögren's syndrome (pSS) and its assessment relies on both objective measurement of residual secretion and subjective symptoms reported by patients. However, while the objective assessment and grading of glandular dysfunction can be easily performed, the spectrum of clinical symptoms encompassed by the terms 'dry eye' and 'dry mouth' is wide and heterogeneous. Therefore, patient-reported outcomes (PROs) for dryness in pSS poorly correlate with the amount of glandular secretion. In addition, subjective dryness is not correlated with the severity of systemic disease and severely affects the patient quality of life even in presence of active extraglandular manifestations. The purpose of this review article is to provide an overview of glandular dysfunction in pSS as well as the impact of discrepancy between objective assessment, subjective symptom and extraglandular disease activity on disease management.

Introduction

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease recognising exocrine glands as the main target (1). Although signs and symptoms of mucosal dryness dominate the clinical picture, the systemic nature of the disease accounts for extraglandular manifestation experienced by up to a half of patients overtime (2). Therefore, the spectrum of pSS encompasses a wide range of conditions ranging from mild xerophtalmia to purpura, vasculitis, peripheral neuropathy and eventually lymphoma, the latter representing the most severe complication of the disease (3, 4). On this basis it could be reasonably arguable that disease activity, as defined by the burden of extraglandular manifestations would represent the major determinants of poor quality of life (QoL) in pSS patients with active disease. However, recent data ruled out this hypothesis revealing that patient-reported symptoms such as dryness, pain and fatigue are those affecting the most QoL in pSS (5). Furthermore, the discrepancy between subjective symptoms related to glandular impairment and objective measurements of glandular output as well as the evidence that disease activity indexes and patient-reported outcomes (PROs) do not align impose to reconsider inclusion criteria and endpoints for future clinical trials. The purpose of this review article is to provide an overview of glandular dysfunction in pSS as well as the impact of discrepancy between objective assessment, subjective symptom and extraglandular disease activity on disease management.

The normal tear film and pSS dry eye disease

In normal conditions, the aqueous part of the tears is constantly produced by the lacrimal glands. Blinking allows fresh tears to move from the upper and lower marginal menisci and to form a film while ensuring that a fresh oil component is constantly drawn from the meibomian glands and that mucus is spread over the epithelial surface (6, 7). Upon secretion by the acinar epithelium, tears are isotonic with serum and the electrolyte content mainly depends on sodium, potassium, chloride and to a lesser extent on magnesium and calcium. The normal tear osmolarity is 309 mOsm/liter and the average pH is 7.25 (8). As far as tear proteins

Table I. Patient-reported outcomes used to assess dryness and related symptoms.

	Xerostomia inventory Thomson et al. [24]	Ocular surface disease index Schiffman et al. [23]	Liverpool sicca index Field et al. [22]	Sicca symptoms inventory Bowman et al. [25]	EULAR Sjögren's syndrome patient-reported index Seror et al. [26]
Year	1999	2000	2003	2003	2011
Number of items	11	12	28	10	3
Number of domains	1	1	5	4	3
Domains (number of items)	Dry mouth symptoms*	Dry eye symptoms	Oral symptom (8) Oral symptom control (5) Sensory (4) Ocular (7) Sexual function (4)	Oral dryness (5) Ocular dryness (3) Vaginal dryness (1) Cutaneous dryness (1)	Dryness (1) Pain (1) Fatigue (1)
Correlation with disease activity indexes	NA	NA	NA	NA	No correlation with ESSDAI

*Within the domain, 4 questions explore nose, eye, nose and skin dryness. ESSDAI: EULAR Sjögren's syndrome disease activity index. Numbers in square brackets indicate the corresponding reference in the manuscript.

are concerned, lysozyme, lactoferrin and lipocalin are secreted by the acinar tissue of the lacrimal gland while resident plasma cells secrete IgA. The oil secreted by the meibomian glands and, to a lesser extent by the glands of Zeis in the eyelids, contains several phospholipids, mainly phosphatidylcholine and phosphatidylethanolamine, along with wax esters and cholesterol esters. This lipid layer contributes to the stability of the tear film by slowing down the evaporation of the aqueous component (9). Finally, mucus contains large glycoproteins (mucins) with a very high carbohydrate content. Water soluble mucins are produced by goblet cells and constitute a gel which is bound to the other layers by epithelial mucins to ensure further lubrication of the film. The tear film has three main functions: i. to nourish the corneal epithelium, which is lacking of blood vessels, acting as a coupling medium for oxygen from the air; ii. to protect the eye being both a physical barrier and an antibacterial substance (e.g. through lysozyme and secretory IgA); iii. to improve the quality of the retinal image by smoothing out irregularities of the cellular surfaces (7). The tear film is a dynamic and complex structure made of different components which balance and interaction is crucial to keep it stable. On this basis, dry eye can recognise two different etiologies: i) aqueous-deficient dry eye results from

a primary secretory dysfunction of lacrimal glands (e.g. due to an inflammatory infiltrate that disrupts the glandular parenchyma); ii) evaporative dry eye is the consequence of abnormalities of the lipid or mucin layer integrity and is the consequence of meibomian gland dysfunction and goblet cell loss respectively (10). The dysfunction of meibomian glands can be the consequence of many conditions, including treatment with retinoid acid for acne or with hormone replacement therapy during menopause. However, being exocrine glands they can also can be a target of pSS, be infiltrated by immune cells and eventually damaged (11). Likewise, the inflammatory infiltration of the conjunctival stroma could determine damage and loss of goblet cells (12). Therefore, dry eye in pSS can be due to either a deficiency of aqueous secretion, an impairment of the lipid layer, an impairment of the mucin gel or a combination of the three (13). In addition, pro-inflammatory cytokines secreted in the tear fluid may play an important role in the development of dry eye and its complications in pSS (14). In particular, increased levels of IL-17, IL-6 and interferon (IFN)-γ, have been described in pSS tears compared to normal tears and data from animal model suggest that while IL-17 plays a role in corneal barrier disruption through the stimulation of matrix metalloproteinases, IFN-γ may pro-

mote goblet cell loss and epithelial apoptosis (15). The diagnostic tests currently employed to assess patients with symptoms suggesting dysfunctional tear syndrome are many. The Schirmer's test quantitatively measures the tear production either in normal conditions or upon stimulation of the lacrimal reflex arc. Epithelial staining with vital dyes (namely dyes that stain degenerating or dead cells) such as Rose Bengal, lissamine green and fluorescein explore the presence of abnormalities of the eye surface, stability of the tear film and the severity of secretory impairment. The tear film breakup time evaluates the stability of the tear film by measuring the time required for the tear film to break up following a blink. Values of less than 5 mm of strip wetting in 5 minutes (<15mm upon stimulation) of the Schirmer's test, dye accumulation in corneal areas upon epithelial staining and a tear film break up time of less than 5–10 seconds support the diagnosis of dysfunctional tear syndrome. Additional tests such as the assessment of tear osmolarity and meibomian gland dysfunction as well as impression cytology can also be performed (8). After being diagnosed, the dry eye should be graded according to the presence of symptoms without corneal lesions (grade 1), with epithelial erosion, punctate keratopathy and/or filamentary keratitis (grade 2) or with permanent sequelae such as cor-

neal ulcer and opacity in addition to the lesions of 2 (grade 3).

The normal salivary secretion and its impairment in pSS

Saliva is a solution consisting of 99% of water and 1% of proteins and electrolytes and resulting by the secretion of paired major salivary glands as well as minor salivary glands (MSGs) (16). The main functions of saliva are: to protect oral and perioral tissues, by providing both adequate lubrication and antimicrobial/cleansing activity, to facilitate eating and initiate digestion, to facilitate speech, to maintain the homeostasis of oral microbiota. Major salivary glands account for over 90% of secretion and among these, the submandibular glands provide over 60% of the secretory product. Parotid glands provide about 20% and sublingual about 10% while the 600–1000 MSGs are widespread in the oral cavity and contribute for the remaining 10% of the total salivary production. Due to their serous nature, parotid glands provide the aqueous part of saliva containing amilase, solphomucins and sialomucins. Conversely, submandibular glands display a variable combination of serous and mucous secretory units and secrete a viscous fluid mainly containing glycoproteins sulphated cystatins and neuronal and epidermal growth factors. Finally, sublingual glands and MSGs glands are mainly mucous. Being the major contributors to salivary production, submandibular glands ensure an adequate lubrication of the oral cavity. However, due to their anatomical distribution, MSGs seems to provide a more effective and widespread lubrication although the overall amount of their secretion is consistently lower (17). In addition, MSG secretory product includes consistent amounts of IGs, mainly IgA, salivary acid phosphatase and lysozymes which exert a crucial protective role against infection and protect tooth enamel preventing the development of caries. In normal conditions and at rest 0.4–0.5 ml of saliva per minute are produced but in presence of specific stimuli (*e.g.* mechanical, gustatory, olfactory, or pharmacological) this output can increase to up to 3ml/min-

ute. (18). Reduced salivation has been associated to reduced mouth clearance since a smaller bulk of secretion and the lack of a mechanic action of saliva allows the food to be trapped on the vestibular surfaces of the teeth. This, together with a reduced capacity to buffer oral pH after meals and snacks, increases the risk of caries and eventually progressive tooth loss. To note, caries are not only more frequent in pSS but also occur in unusual sites such as the lingual surface and the teeth cusps (19). Reduced salivary secretion also accounts for the development of oral mucosal lesions and fungal infections, mainly candidiasis involving tongue, palate and perioral areas, as well as for impaired chewing and swallowing with subsequent avoidance of specific food and nutrient deficiency (*e.g.* vitamin C from citrus fruits) (20). Salivary flow can be easily measured in clinical practice both at rest and upon stimulation (*e.g.* chewing). Salivary gland hypofunction is considered as whole unstimulated saliva <0.25 ml/minute, whole stimulated saliva <0.7 ml/minute or both (18)

Objective secretory impairment versus subjective dryness

If the objective assessment and grading of glandular dysfunction can be easily performed as detailed above, the spectrum of clinical symptoms encompassed by the terms 'dry eye' and 'dry mouth' is wide and heterogeneous (21). Eye dryness is associated with foreign body/grit sensation, burning, itching, pain, redness, photophobia and blurred vision, while mouth dryness is associated with burning, glossodynia, dysgeusia, dysphagia and impaired speech (12, 22). Therefore, the quantification of symptoms related to secretory impairment in pSS requires PROs encompassing all the above mentioned domains and also including other aspects like intimacy, in order to ensure that the overall impact on the QoL is captured. The first PRO, the Liverpool sicca index, was developed and validated in early 2000 (23). All sicca-related PROs available at that point, such as the xerostomia inventory or the ocular surface disease severity index, were focused on

either ocular or oral domains, but not both and did not explore other domains (24, 25). The Liverpool sicca index and the following Sicca Symptoms Inventory (SSI) explored in detail many facets of dryness hence providing a wide picture of the patient perspective. SSI, both its long and short form, also allowed a better discrimination of patients with pSS from non-SS sicca controls (26). In 2011, the European League Against Rheumatism (EULAR), validated a novel PRO, the EULAR Sjögren's syndrome patient-reported index (ESSPRI) to be easily implemented in clinical trials and clinical practice. ESSPRI includes dryness together with pain and fatigue (as derived by the previously used Profile of Fatigue and Discomfort (PROFAD) questionnaire) which are quantified on a 0–10 visual analogic scale (Table I) (27, 28).

A first critical aspect with regard to the PROs for dryness in pSS is that their correlation with objective measurements of glandular function is poor. In more detail, this correlation is even weaker for ocular than for oral dryness. As recently pointed out by Bowman *et al.*, pSS patients report perceived dryness according to their symptom sensitivity and this ranges from stoical (underestimation of dryness compared to moderate to severe impairment of secretion at objective tests), to accurate, to sensitive (overestimation of dryness with mild impairment of secretion at objective tests). In addition, in the same patient ocular and oral symptom sensitivity correlate fairly well (29). It is interesting to note that the stoical phenotype was more frequently observed in older patients with more severe disease allowing to speculate that they develop a better capability to cope with the dryness overtime. However, dryness and dryness-related symptoms remain a major concern in pSS patients and have been recently added in the list of strongest factors associated with QoL together with pain, depression, anxiety, and fatigue (5). As demonstrated by a Japanese study, presence and extent of dry eye of any aetiology significantly and negatively impacts on subjective happiness (30), while dry mouth is defined "an aggra-

vating misery" by patients, due to its dramatic impact on multiple domains of well-being (31).

Subjective dryness versus extraglandular manifestations of the disease

Owing to its systemic nature, pSS is also characterised by a wide spectrum of extraglandular manifestations that can virtually affect any organs. In this regard, EULAR recently developed a comprehensive disease activity index encompassing and weighting different domains than can be affected by pSS. The EULAR Sjögren's syndrome disease activity index (ESSDAI) has now been validated and proven to be subjective to change if employed to monitor the efficacy of therapeutic approaches (28). However, when exploring the impact of disease activity on QoL in pSS, this is significantly less compared with subjective symptoms, as quantified with the ESSPRI) even in patients with moderate-to-high systemic activity (5). As a matter of fact, ESSDAI and ESSPRI are not at all correlated with each other (32). This evidence deserves particular attention in light of the evidence gathered so far from clinical trials in pSS. Over the last years, a mutual effort from pSS investigators across Europe allowed to demonstrate that some biologic agents, such as rituximab (RTX), belimumab and abatacept, are effective in improving extraglandular manifestation of pSS and therefore they are able to significantly reduce disease activity in this disease (33, 34). However, when observing their effect on the glandular side, it is surprising to note that despite their capability to interfere with cellular infiltrate (35, 36), the subsequent improvement of objective glandular function and dryness symptom is poor, if any. It became therefore evident that an important patient need remains unmet and that although we can deal with severe disease manifestations and improve prognosis, we cannot improve QoL as effectively. Furthermore, the use of both ESSDAI and ESSPRI as primary endpoints in clinical trials as well as tools in daily practice should be recommended in order to capture the overall picture of each pSS patient.

In this regard, an important step forward has been made by Seror et al., who recently proposed cut-off values for ESSDAI and ESSPRI. In particular, data from 2 large pSS patient cohorts, one from a French collaborative project and another one from an European consortium, provided cut-off values able to define disease activity levels, minimal clinically important improvement (MCII) and patient acceptable symptom state (PASS) to be employed in future clinical trials (37). This represents a major achievement in the path towards the harmonisation of inclusion criteria as well as endpoints across studies and will allow to better understand and compare the impact of therapeutic approaches on glandular related manifestations and eventually on the quality of life. Another interesting aspect in this regard is that qualitative changes in saliva and tears may be more informative than quantitative measurements of the glandular output. In fact, as detailed above, these are two heterogeneous fluids with different physical characteristics that cannot be captured by flow measurements alone (38). Therefore, novel technology ensuring a comprehensive evaluation of salivary and tears components, such as proteomics and liquid chromatography-mass spectrometry, are promising tools to explore in more detail the abnormalities of secretory products in pSS and how they impact on perceived symptoms (39, 40).

Concluding remarks

In conclusion, the discrepancy between PROs, objective measurement of glandular function and systemic disease activity indexes in pSS demonstrates that they provide unique and complementary perspectives to be explored and integrated in clinical practice. The plethora of symptoms and complications related to impaired glandular function severely affect the QoL and the identification of effective therapeutic strategies is compelling. Therefore, the design of future trials to explore new compounds in pSS should be performed based on this evidence and in order to avoid that an acceptable QoL remains a major unmet need.

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