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Research Article

Effects of Tear Osmolarity on Tear Mucin Layer in Patients with Hypothyroidism, Sjögren's Disease and Rheumatoid Arthritis

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Abstract

Objectives: To describe the association between tear film osmolarity and mucin layer alterations in patients with hypothyroidism, Sjögren's disease and rheumatoid arthritis.

Methods: Cross-sectional study with a sample of 44 patients, obtained from clinical records of patients with diagnosed hypothyroidism, Sjögren's disease and/or rheumatoid arthritis, and complete dry eye disease assessment. We evaluated tear osmolarity by means of the Tear Lab system and tear mucin layer by means of the ferning test using Rolando's classification.

Results: 63.7% of the sample had an abnormal ferning test and 81.8% of the sample was found to have tear film hyperosmolarity. Among the group of patients with abnormal ferning tests, 82.1% had hyperosmolar tears.

Conclusion: Patients with hypothyroidism, Sjögren's disease and rheumatoid arthritis, are proven to have a tear profile that includes hyperosmolarity and tear mucin layer abnormalities according to tear ferning test.

Keywords: *Dry Eye; Osmolarity; Mucin, Hypothyroidism; Sjögren's Disease and Rheumatoid Arthritis*

Introduction

As stated in the TFOS DEWS II report in 2017, "Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles" [1]. This definition encompasses the fact that inflammation and hyperosmolarity are part of the cycle that results in tear film instability.

The disease's signs and symptoms are therefore result of homeostasis loss in the tear film involving any of its three layers due to lacrimal functional unit dysfunction; made up by ocular surface tissues, neuronal connections and lacrimal secretory machinery [2]. This last component, the lacrimal secretory machinery, includes conjunctival goblet cells acting as active secretors of gel-forming mucins that make up the mucinous constituents of the tear film.

Tear osmolarity has been considered as an index indicating the balance of complete tear dynamics; distribution, turnover and elimination [3]. Evidence conclusively shows that hyperosmolarity drives morphological changes on the ocular surface [4] and affects different cell populations [5] through direct cell apoptosis or indirect inflammation cascades, among the victims are goblet cells immersed in conjunctival epithelium which are in charge of producing the bulk of the mucinous components of the tear film, which, for the purpose of this work, will be assessed by means of the tear ferning test; a test that analyses fern pattern formation amid various factors, involving mucins, salt and proteins [6].

High prevalence of the disease has been calculated according to different population studies [7], and its symptoms decrease significantly the quality of life of patients who suffer it [8]. It is estimated that up to 25% of ophthalmological visits are related with this disease, this makes it a growing public health concern [9].

Autoimmune disease is a term that comprises mainly systemic disorders in which a person's immune system produces dysregulated responses against self-produced antigens - autoantigens. It is currently estimated that the worldwide prevalence of autoimmune diseases ranges between 7.6 and 9.4% [10]; dry eye disease relationships with these types of pathologies has come a long way, considering that in the 90s dry eye disease was described exclusively in patients with Sjögren syndrome [11]. Nowadays it is known that dry eye disease is found not only in Sjögren syndrome but also as part of other autoimmune disorders such as rheumatoid arthritis [12].

Yet, Sjögren syndrome is heavily associated with dry eye disease considering that one out of ten patients presenting with clinically significant disease have underlying Sjögren syndrome [13].

Among the aforementioned multifactorial etiology of dry eye disease, not only autoimmune disorders play a part in the pathogenic cycle, thyroid hormone imbalance itself also takes part in it taking into account the presence of nuclear receptors for thyroid hormones in the ocular surface [14] and considering that low hormone input has direct effects on lacrimal gland and corneal epithelium [14,15].

All of the disease entities previously described have a particular relationship through gender; thyroid disease occurs more frequently in women [16], autoimmune diseases mentioned are far more frequent in female population [17-19], and there is a gender deviation towards females among risk factors for dry eye disease [20].

This paper intends to show tear film osmolarity and mucin layer changes by means of tear ferning testing in patients with dry eye disease and hypothyroidism, rheumatoid arthritis and Sjögren syndrome. As mentioned before, the relationship between dry eye disease and the pathologies to study is known, yet tear film dynamics haven't been evaluated in a group of said patients. These changes might be useful to direct diagnostic attention to these populations and address them specifically as part of disease treatment.

Materials and Methods

The study protocol was approved by the Ethics in Investigation Committee of the Fundación Universitaria Sanitas.

We performed a cross-sectional study for seven months (June - December 2014) with patients older than 40 years old that had a diagnosis of dry eye disease according to symptoms, clinical signs and tests. Demographic data is described in table 1. The sources of this information were the clinical records of patients attending the Ocular Surface Department of the Sociedad de Cirugía Ocular in Bogotá, Colombia. A total of 44 patients with clinical history of Sjögren's, rheumatoid arthritis and/or autoimmune hypothyroidism were diagnosed with dry eye disease. The data of both eyes of each patient was analyzed.

Characteristics	n = 44 (%)
Age	
Average (SD)	60.15 (± 11.8)
Gender	
Female	39 (88.6)
Male	5 (11.4)
Disease Diagnosis	
Hypothyroidism	31 (57.4)
Sjögren's	19 (35.2)
Rheumatoid Arthritis	4 (7.4)
Oxford Grading System	
Negative	28 (63.6)
Grade I	11 (25.0)
Grade II	4 (9.1)
Grade III	1 (2.3)
Tear Ferning Test (Rolando Classification)	

II	16 (36.3)
III	27 (61.4)
IV	1 (2.3)
Osmolarity	
Normal	8 (18.2)
≥ 308 mOsm/L (mild)	14 (31.8)
≥ 320 mOsm/L (moderate)	19 (43.2)
≥ 340 mOsm/L (severe)	3 (6.8)
OSDI Score	
Normal (0 - 12)	6 (13.6)
Mild (13 - 22)	10 (22.7)
Moderate (23 - 32)	7 (15.9)
Severe (33 - 100)	21 (47.7)

Table 1: *Characteristics of the sample studied.*

Dry eye disease diagnosis is based on multiple tests as well as clinical assessment. In our study we included patients with established diagnosis of dry eye disease, previously made by examining the following variables in the patient's first visit: 1. OSDI Questionnaire assessment, 2. Tear film analysis through Schirmer Test type 1, tear break-up time (BUT), osmolarity measurements, meniscometry, ferning test using the classification system proposed by Rolando, and 3. Ocular surface evaluation with lissamine green staining (Oxford grading system). Patients with history of laser refractive surgery or incisional surgery were excluded from this study.

A validated Spanish translated version of the OSDI questionnaire was applied evaluating 3 sections: a. physical symptoms, b. alteration in the performance of daily activities and c. problems with environmental factors, each section gives a score which is added to obtain a total result and thus establish a classification of the degree of dry eye (mild-moderate -severe). A score lesser than or equal to 13 indicates normality, a score between 13 - 22 mild disease, 24 - 50 moderate disease, and greater than 50 severe disease [21].

For Schirmer test type 1, we inserted into the outer third of the lower bulbar conjunctiva the end of a strip of blotting paper, allowing it to be impregnated with tears for 5 minutes, after this time the length of the moistened strip is measured. Normality for Schirmer type 1 test is between 5 and 15 mm and less than 5 mm establishes dry eye diagnosis [21]. BUT consists of instilling fluorescein in the ocular surface to allow the visualization of the tear film and to measure the time it takes to break between blink, this exam is done under the slit lamp with cobalt blue filter. Normal values for BUT are considered to be greater than 10 seconds [21].

Tear film osmolarity was measured using the TearLab Osmolarity System developed by TearLab Corp (San Diego, Ca, USA); an osmometer which is used to retrieve a small amount of tear from the inferior meniscus with a microcapillary connected to a chip that quantifies the osmolarity directly from impedance measurements. Meniscometry was done in a slit-lamp by measuring tear meniscus height when stained with fluorescein. For the ferning test a sample of 1 µL of tear was taken from the inferior tear meniscus with a microcapillary, the sample was put in a glass slide and allowed to air-dry afterwards for ten minutes, using microscopic visualization under 10x magnification, ferning patterns of the samples were classified according to the Rolando classification [22]. The ocular surface was assessed with lissamine green staining by means of the Oxford classification for dry eye disease [23] (Table 3).

Classification according to the patient's disease was carried out in 3 groups only: hypothyroidism, Sjögren's disease and rheumatoid arthritis, as a result of the descriptive analysis of the population. Our sample included patients with more than one diagnosis, and these are addressed differently as shown in table 3.

The tests applied were performed in the following order: 1. OSDI Questionnaire, 2. Tear film osmolarity, 3. Ferning test, 4. Meniscometry, 5. Schirmer test type 1, 6. BUT, 7. Lissamine green staining.

All the results of tests applied during consultation for dry eye disease diagnosis were integrated into a pre-established form used for every patient that attends the Ocular Surface Department of the institution. Values considered as normal and abnormal considered for each test are presented in table 2.

Test	Cutoff Values	Evaluated Aspect
Schirmer Test 1	Abnormal ≤ 10 mm	Tear production
Tear Break-up Time (BUT)	Abnormal ≤10 sec	Tear film instability
Lissamine Green Staining	Grade 0 - Negative Grade I - Mild Grade II/III - Moderate Grade IV - Severe	Ocular Surface Disturbance
Osmolarity	Hyperosmolarity ≥ 308 ml/Osm	Tear film instability
Meniscometry	Abnormal ≤ 3 mm	Tear volume
Rolando Classification for Tear Ferning Test	Normal stage I - II Abnormal stage III - IV	Tear mucin layer
OSDI Questionnaire	Normal 0 - 12 Mild 13 - 22 Moderate 23 - 32 Severe 33 - 100	Objective symptoms

Table 2: *Abnormal cutoff values for tear film and ocular surface analysis.*

Data analysis was performed using measures of central tendency and dispersion according to the level of variable measurement.

Results

We obtained data corresponding to 44 patients (Table 1) with an average age of 60 (SD ± 11) years, of which 88.6% (n = 39) of the patients were women and 11.4% (n = 5) men. The most frequent disease was hypothyroidism with 22 patients (50%), followed by Sjögren's disease with 10 patients (22.7%) and 2 patients with rheumatoid arthritis (4.5%). 8 patients shared the diagnosis of thyroid disease and Sjögren's, 1 shared the diagnosis of hypothyroidism and rheumatoid arthritis and 1 shared the diagnosis of rheumatoid arthritis and Sjögren's, for a total of 10 patients with more than one autoimmune disease diagnosis (22.7%). Table 3 summarizes this information.

Characteristic	Group Disease					
	Hypothyr*	Sjögren's	Rheumatoid Arthritis	Hypothyr* and Sjögren's	Rheumatoid Arthritis and Sjögren's	Hypothyr* and Rheumatoid Arthritis
	n = 22 (%)	n = 10 (%)	n = 2 (%)	n = 8 (%)	n = 1 (%)	n = 1 (%)
Age						
Average (SD)	60 (±11)	59 (±12)	61 (±17)	61(±11)	45	67
Gender						
Female	20 (90.9)	8 (80)	2 (100)	7 (87.5)	1(100)	1(100)
Male	2 (9.09)	2 (20)		1(12.5)		
Oxford Grading System						
Negative	13 (59.06)	8(80)	2 (100)	3(37.5)	1(100)	1(100)
Grade I	8 (36.3)	1 (10)		2(25)		
Grade II	1 (4.54)	1 (10)		2(25)		
Grade III				1(12.5)		
Tear Ferning Test						
II	8 (36.3)	3 (30)	1 (50)	4(50)		

III	14 (63.6)	6 (60)	1 (50)	4(50)	1(100)	1(100)
IV		1 (10)		-		
Osmolarity						
Normal	3 (13.6)	3 (30)		2(25)		
≥ 308 mOsm/L (mild)	7 (31.8)	3 (30)	1 (50)	1(12.5)	1(100)	
≥ 320 mOsm/L (moderate)	11 (50)	3 (30)	1(50)	4(50)		1(100)
≥ 340 mOsm/L (severe)	1 (4.54)	1 (10)		1(12.5)		
OSDI Score						
Normal (0 - 12)	3 (13.6)			3(37.5)		
Mild (13 - 22)	5 (22.7)	2 (20)	2 (100)	1(12.5)		
Moderate (23 - 32)	2 (9.09)	3 (30)		4(50)		
Severe (33 - 100)	12 (54.5)	5 (50)		1(12.5)	1(100)	1(100)

Table 3: *Patient's characteristics according to disease.*
**Hypothyroidism.*

Among the group of patients, 63.6% had a tear ferning test classified as III or IV according to Rolando's classification (Table 2) and 81.8% had a tear film osmolarity higher than 308 mOsm/L. Likewise, out of these patients with abnormal tear ferning patterns, 82.1% were found to have tear hyperosmolarity.

In patients with hypothyroidism, we found an abnormal ferning test in 63.6% (n = 14) and an elevated tear film osmolarity in 86.3% (n = 19) of the cases. 70% (n = 7) of patients with Sjögren's syndrome had mucin layer abnormalities while tear film hyperosmolarity was found in 70% (n = 7). Among patients with rheumatoid arthritis, 50% (n = 1) showed an abnormal ferning test, and all of the cases showed tear film hyperosmolarity.

In the group of patients with shared diagnoses: all of them are women with an average age of 57 years. From the group of patients with hypothyroidism and Sjögren's, half (n = 4) had a tear ferning test classified as III and moderate hyperosmolarity; all patients with Sjögren's and rheumatoid arthritis had tear ferning test altered with mild hyperosmolarity and all patients with thyroid disease and rheumatoid arthritis had a tear ferning test classified as III with moderate hyperosmolarity.

Regarding self-reported symptomatology, 85.71% of patients in the whole sample presenting with abnormal tear ferning tests and 86.11% of patients presenting with an abnormal osmolarity test were found to have OSDI questionnaire scores above what is expected as normal.

Discussion

Dry eye disease is more common in patients with autoimmune diseases than in patients without them [20] yet tear film dynamics haven't been evaluated specifically in patients with said characteristics. Taking into account that these diseases are considered as immune disorders mediated by inflammatory responses [24] and that inflammation has been regarded as one of the most important components in the pathogenesis of dry eye disease [25], it is this inflammatory response that provides a link between both pathological processes.

Our study clearly demonstrates that the parameters we established are indeed altered in patients with the pathologies described. For instance, only 18.2% of the patients in the sample had iso-osmolar tears at the time of diagnosis, which means that over 80% of the

sample had some degree of hyperosmolarity, a characteristic that Baudouin., *et al.* described as the causing agent of decreasing goblet cell density in patients with dry eye disease [26]; which would explain tear mucin layer alterations due to this proinflammatory toxic cellular environment.

Our results also show that ferning patterns are altered in 63.6% of the patients in the sample without great variations between subgroups according to a specific disease. This fact takes relevance when examining the osmolarity values in the tears of these same patients; 82.1% were found to have tear hyperosmolarity. This association between tear film osmolarity and tear ferning patterns is explained in the work by Masmali., *et al*. who state that the shift in the salt-to-macromolecule ratio explains ferning quality because of the combination of raised solutes in the solution that is the tear film and the reduced concentration of proteins and mucins in it [6]. Equally, only 36.3% of our sample showed a normal ferning pattern graded as II or less and, in this subgroup, only 17.8% presented with tear hyperosmolarity. Our data has a certain degree of heterogeneity because of the intrinsic nature of dry eye disease as a multifactorial and etiologically plural entity [27].

The results previously stated establish that tear mucin layer according to ferning patterns are correlated with the osmolarity in the tear film of patients with hypothyroidism, Sjögren's disease and rheumatoid arthritis. According to this analysis, both tear film osmolarity and ferning patterns have clinical relevance in this type of patients. It would be essential then to address these issues during the symptomatic treatment of said patients.

When examining our sample as a whole we found that patients with altered osmolarity and tear ferning results commonly score higher than normal in the OSDI questionnaire, which further relates to the importance of subjective symptoms reported by patients in relation to possible outcomes in clinical evaluation.

From our data we established that symptoms of dry eye disease as evaluated by the OSDI Questionnaire are regarded more commonly as severe rather than lesser grades in patients with autoimmune thyroid disease and Sjögren's syndrome, which may mean that eye care physicians should be aware about this population. It was recently described that particularly in Sjogren's there is a positive correlation between hyperosmolarity, OSDI scores and ocular surface staining [28], meaning that in these patients clinical signs are highly suggestive of self-reported symptoms.

As a more general finding, our data is provided by a sample out of which 88.6% are women, a fact that encloses one of the key epidemiologic aspects both on dry eye disease and autoimmunity, bearing in mind that research has shown an increasing association between female sex and pathologies studied [14,18].

In view of our findings, it's worth noting that patients with characteristics similar to the ones in our sample have to be screened for tear hyperosmolarity because this result could indirectly provide us with information about the tear mucin layer in these population and guide optimal dry eye treatment. Even though hypo-osmolar formulations are already regarded as superior to lubricants with higher solute per solution ratio [29], in patients with autoimmune disease it is critically important not only to assess the aqueous component of the tear film but the mucinous one as well. Furthermore, bearing this idea in mind, newer molecules working as mucin secretagogues that have been studied as treatment for dry eye [30-33], appear as an options worth considering.

Conclusion

More studies are needed to draw further conclusions; using a bigger sample, including other autoimmune diagnosis and taking into consideration variables such as time from diagnosis and patient's systemic treatment. There is ample space for growing investigation on this topic; for instance, a comparison between tear profiles of patients with autoimmune disease and patients without it is yet to be made.

In summary, our work identifies a relation between tear film hyperosmolarity and mucin layer alterations in patients with autoimmune disease considering that both of these features are more commonly altered in this population.

Conflict of Interest Statement

The authors declare no conflict of interest.

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