

Characterization of Meibomian Gland Dysfunction in Patients with Rosacea

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Abstract

Background: Rosacea frequently involve the eyes with impact on life and vision quality. There are gaps in the understanding of ocular involvement, specially related to eyelid glands, which share common features to sebaceous glands.

Purpose: Describe ocular surface disease related to Rosacea and its associations.

Methods: Ninety-three individuals were selected to this cross-sectional, observational, non-interventionist study, divided into groups: rosacea (n=40) and controls (n=53). We investigated objective parameters of the ocular surface (conjunctival hyperemia, tear film stability and volume, meibomian gland dysfunction, dry eye disease, ocular surface staining) comparing healthy individuals with rosacea patients.

Results: 69.23% of rosacea group were women, mean age of 47.34 ± 12.62 years old. Compared to matched controls there was no statistically significant differences regarding to visual acuity ($p=0.987$) and tear film parameters (tear meniscus height ($p=0.338$), non-invasive tear film rupture time (NIBUT) ($p=0.228$), invasive rupture time (TBUT) ($p=0.471$) and Schirmer's test ($p=0.244$)) as well as conjunctival hyperemia ($p = 0.106$), and fluorescein staining ($p = 0.489$). Significant association was found in meibography evaluation ($p = 0.026$), mucous layer integrity ($p = 0.015$) and ocular surface symptoms ($p < 0.0001$). Rosacea patients also showed important eyelid changes: glandular expressibility ($p < 0.001$), glandular secretion pattern ($p < 0.001$) and telangiectasia ($p < 0.001$) compared to controls.

Conclusion: Meibomian gland dysfunction is frequently associated to dermatologic conditions and is characterized by morphological findings in the meibography as well as lipid secretion impairment that lead to evaporative dry eye and ocular surface dysfunction and inflammation.

Background

Rosacea is a chronic inflammatory skin disease, characterized by major and secondary cutaneous signs that include flushing, telangiectasia, papules, pustules, and ocular manifestations. Multiple features may be present in the same patient but the first standard classification suggested by the National Rosacea Society Expert Committee in 2002 is still used for didactic purposes, separating the disorder into four subtypes: erythematotelangiectatic, papulopustular, phymatous and ocular rosacea.(1–3)

Ocular involvement is frequent, but often overlooked in patients with Rosacea.(4) Around 58 to 72% of all patients present ocular complications related to the disease, usually described as mild and nonspecific.(4, 5) In this scenario, when skin findings are not remarkable, ocular rosacea may be misdiagnosed with other eye conditions.(4) Patients can experience ocular burning, itching, redness, photophobia and foreign body sensation.(6, 7) Objective signs that strongly suggest ocular rosacea are lid margin telangiectasia, interpalpebral conjunctival injection, spade-shaped infiltrates in the cornea and scleritis/sclerokeratitis.(8) Lid disease-related manifestations, as blepharitis and meibomian gland dysfunction, are the most common presentations, but abnormal Schirmer test and corneal involvement were reported in more than

one third of the cases.(9) Less specific findings such as conjunctivitis, collarettes around lashes, abnormal meibomian secretion and evaporative tear dysfunction also seem to be common but poorly detailed.(4, 5, 9) In this context, ocular surface disease related to Rosacea remains poorly described.

This study aims to evaluate ocular surface findings in Rosacea patients, quantifying symptoms and measuring objective ocular surface parameters. Furthermore, correlations between ocular manifestations and cutaneous disease presentation would provide a better understanding of the full disease spectrum that may help, ophthalmologists and dermatologists to provide proper care of this complex disease.

Methods

This is a cross-sectional, observational, non-interventionist study. Forty rosacea patients were included along with 53 healthy controls, paired by age and sex. Participants were recruited from dermatology and ophthalmology outpatient clinics at University of Campinas (UNICAMP) between 2017 and 2019. Individuals with other ocular surface diseases, such as sequelae of trachoma and herpetic keratitis and other dry eye conditions, as Sjogren's syndrome were excluded. This study was carried out with the approval of the Institutional Research Ethics Committee Board of the University of Campinas (UNICAMP). Written informed consent was obtained from all subjects before procedures were performed.

Classification and Rosacea staging was based on the report of National Rosacea Society Expert Committee as well as Dermatological Life Quality Index (DLQI) and performed by a dermatologist. All cases underwent detailed ophthalmological examination as described below and performed in this sequence.

After a comprehensive ocular anamnesis, dry eye symptoms were evaluated using the ocular surface disease index (OSDI) questionnaire. The OSDI score ranging from 0 to 100 and values below 12 are considered normal.(10,11)

The ocular surface parameters analyzed were described as follows:

- a. Tear meniscus height (TMH): Tear film volume
- b. Non-invasive tear break-up time (NITBUT): tear film stability
- c. Meibography: meibomian gland morphology
- d. Fluorescein staining: corneal epithelial integrity
- e. Lisamine green staining: damaged ocular surface epithelial cells as well as unprotected by mucin or glycocalyx.
- f. Schirmer test: Tear volume

TMH, NITBUT and meibography were obtained by using Keratograph 5M (Oculus, Wetzlar, Germany), a non-invasive equipment developed to assess the tear film and the ocular surface through an objective way and photodocumentation. All procedures were sequentially performed by the same examiner, in accordance with specific guidelines and regulations.(11–14)

Ocular surface disease was classified according to both global consensus of the Tear Film and Ocular Surface Society, Dry Eye Workshop II (TFOS DEWS II) and the International Workshop on Meibomian Gland Dysfunction. Table 1 summarizes parameters and cutoff values to discriminate the two main subtypes of dry eye, aqueous deficient (low tear volume) and evaporative dry eye (lipid deficient). Patients with OSDI score ≥ 13 and non-invasive tear film breakup time < 10 s or corneal staining > 5 spots or conjunctival staining > 3 were considered to have dry eye. Those diagnosed with dry eye and that had tear meniscus height $\leq 0,2$ mm were classified as aqueous tear deficiency and ones with meiboscore grade ≥ 1 were classified as meibomian gland dysfunction and evaporative dry eye. Patients who met both criteria were classified as mixed form of dry eye.(11,14,15)

Statistical analyses

Exploratory data analysis was performed using descriptive statistics (mean, standard deviation, minimum, median, maximum, frequency and percentage). Multiple logistic regression was used to assess factors associated with the most frequent types of Rosacea. The level of significance was 5%. The analyses were performed using the computer program STATA 14.0 software (StataCorp LP, College Station, TX, USA).

Ethics Committee Board

This study was carried out with the approval of the Institutional Research Ethics Committee Board of the University of Campinas (UNICAMP) – approval number 80618117.0.0000.5404. Written informed consent was obtained from all subjects before procedures were performed.

Results

Detailed demographic and clinical data of the enrolled patients are shown in Table 2. Most patients were women (69.23%) and mean age was 47 years (range 23 to 75). Patients could present more than one subtype of rosacea, and erythematotelangiectatic presentation was the most common (49%). Only 3 patients (7.5%) had previous diagnosis of ocular rosacea and 1 had exclusive ophthalmological involvement. Regarding the severity of the dermatological findings, 52.5% presented a mild rosacea. The DLQI showed no or minimal impact on patients' life (DLQI ≤ 5) in 62.5% of the cases, although the highest values were related to more severe skin findings ($p = 0.018$). Despite the fact that 62.5% of the patients have reported dry eye symptoms according to OSDI scores, most of them had never sought eye care.

Forty patients diagnosed with rosacea and 53 healthy matched controls were evaluated. Table 3 shows the results of the ocular parameters in each group. Rosacea patients had higher OSDI scores, meibomian gland dysfunction shown in meibography evaluation and mucin layer involvement measured by lissamine green staining compared the non-disease group.

Indeed, according to the global consensus of the Tear Film and Ocular Surface Society (TFOS) Dry Eye Workshop II (DEWS II) and the International Workshop on Meibomian Gland Dysfunction, almost half of rosacea patients (41%) met criteria for dry eye. In this group of Rosacea patients, 62.5% presented evaporative dry eye, 6.25% aqueous deficiency and 31.25% mixed type.

All patients diagnosed with Rosacea in this study had some degree of Meibomian gland dysfunction. Glandular morphology and eye lid evaluation were performed. Meiboscore alterations, telangiectasia and pasty glandular secretion were the most frequent findings. (Table 3). Figure 1 displays positiveness of each parameters evaluated to access dry eye and meibomian gland dysfunction, showing positive criteria ranging from 22 to more than 80%. Comparisons of ocular parameters according to subtypes of rosacea are demonstrated in Table 4.

Additionally, analyzes comparing ophthalmological parameters with rosacea global assessment and treatment were performed showing no relevant associations.

Discussion

Ocular rosacea is considered the most common extracutaneous manifestation of the disease spectrum. Eye signs and symptoms may even precede the cutaneous involvement, affecting ocular surface and meibomian glands, leading to dry eye disease.(4, 5)

Recent publications had shown that patients with rosacea present dry eye noted by lower Schirmer test results, shorter tear film breakup time and higher scores in the Ocular Surface Disease Index (OSDI) when compared to individuals without the disease.(4, 5, 7, 16, 17)

In this cross-sectional cohort of Rosacea patients, ocular surface disease symptoms and meibomian gland dysfunction were frequent findings. Dry eye diagnosis encompasses a broad range of tests to better picture all ocular surface and tear film variations. Herein, dry eye was considered when the patient presented symptoms (OSDI > 13) plus one positive clinical test. Then, dry eye disease is classified as evaporative when it is related to meibomian gland dysfunction, or it is defined as an aqueous deficient when secondary to diminished tear production. Mixed dry eye is also considered. Thereby, this evaluation and classification provided a comprehensive scenario of the ocular surface disease in Rosacea patients. We found positive criteria for ocular surface disease in this group of patients in all parameters evaluated, ranging from 22 to more than 80%. Mostly, Rosacea patients presented meibomian gland dysfunction, positive lissamine green staining, which indicates corneal and conjunctival cells are damaged and higher symptom scores at the OSDI. Of note, there was a high frequency glandular abnormality, observed during expressibility and secretion pattern evaluation of the eyelids margin. Rosacea was associated with ductal

obstruction, telangiectasia and altered glandular secretion, as granular or pasty secretion pattern. In this cohort of patients all subtypes of dry were found. (11, 14)

When clinical forms of the disease were analyzed – erythematotelangiectatic, papulopustular, phymatous and ocular – multiple logistic regression showed that erythematotelangiectatic subtype had the worst scores of OSDI. One bias of the study is that most of the patients with papulopustular subtype of rosacea were in systemic treatment with antibiotics, which also treats ocular manifestations. On the other hand, this finding reinforces the obligation to ask for ocular symptoms in all individuals with rosacea.

Our study highlights the relevance of searching for ocular symptoms. OSDI is a noninvasive screening test to assess ocular surface disease. It is a feasible and no time-consuming questionnaire to apply during dermatological appointment and can be used to identify patients that deserve further ophthalmological evaluation.

As limitations to be acknowledged, we considered the cross-sectional design and unicentric study performed in a tertiary based hospital. However, as main strength of this study, the presentation of systematic ocular assessment evaluation, through a broad panel of tests, comprehensive characterization of all ocular surface parameters and comparisons with the clinical presentation of this complex disease. Literature is scarce in Rosacea association to ocular surface and, to our knowledge, this is one of largest cohorts of rosacea patients submitted to a complete and systematic ocular assessment using the noninvasive technology and a comprehensive set of ocular tests and compared clinical associations of disease. Our study reinforces findings of Palamar *et al* (18) and Machalińska *et al* (19), concerning to the associations of Rosacea and Meibomian gland dysfunction, eyelid abnormalities and dry eye disease. Those conditions might share physio pathological mechanisms and potential therapeutic responses.

Severe forms of ocular surface disease, such as cornea complications secondary to dry eye and inflammation flares, carry a relevant impact on patients' quality of life and vision. In this context, a better understanding of the ocular manifestations related to Rosacea disease is helpful for dermatologists and ophthalmologists. Important findings, such as quantification of symptoms and meibomian gland dysfunctions, were highlighted in our study and may be pursued for a better evaluation of patients. Furthermore, ocular findings could be considered as additional clinical tools in the screening and follow-up of this condition to guarantee ocular surface integrity and prevent complications.

Conclusion

Meibomian gland dysfunction is frequently associated with systemic conditions, but ocular findings remains poorly detailed. It is characterized by morphological alterations in the meibography, such as glandular dropout, as well as lipid secretion impairment. Such disorders may lead to evaporative dry eye, ocular surface dysfunction and inflammation.

List Of Abbreviation

DLQI - Dermatological Life Quality Index

ODSI - Ocular Surface Disease Index

TMH - Tear Meniscus Height

NITBUT - Non-invasive tear break-up time

TBUT – Tear Breakup Time

TFOS - Tear Film and Ocular Surface Society

DEWS II - Dry Eye Workshop II

F – Female

M - Male

Declarations

Ethics approval and consent to participate: This study was carried out with the approval of the Institutional Research Ethics Committee Board (CAAE - 80618117.0.0000.5404). Written informed consent was obtained from all subjects before procedures were performed.

Competing Interest: the authors stated no conflict of interest

Consent for publication: all authors agree

Availability of data and material: datasets and/or analysed available by request

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Auhtor's contribution: Conceived and designed the analysis (MA; AFECT); Collected the data (EBB;CMT; DFLS;LSS); Contributed data or analysis tools (EBB;CMT; DFLS;LSS); Performed the analysis; (MA; EBB), Wrote the paper (MA, EBB; AFECT). All authors have read and approved the manuscript.

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Tables

Table 1 - Dry Eye Disease Diagnostic Criteria

	CRITERIA
Dry Eye Disease	OSDI Score \geq 13 AND Non-Invasive Tear Film Breakup Time < 10s, Corneal Staining > 5 spots, Conjunctival Staining > 3 (10-15)
Aqueous Tear Deficiency	Diagnosis of Dry Eye Disease AND Tear Meniscus height \leq 0.2mm
Meibomian Gland Dysfunction	Diagnosis of Dry Eye Disease AND Meibography grade \geq 1
Mixed Dry Eye	Dry Eye Disease in the presence of Aqueous Tear Deficiency AND Meibomian Gland Dysfunction

Table 2 - Clinical features of Rosacea group

Criteria	N = 40
Age (mean ± SD)	47 ± 12
Sex (M/F)	12/28
Fitzpatrick scale	
1 and 2	25
3 and more	15
Disease grading *	
Erythematotelangiectatic	25
Papulopustular	18
Others (phymatous, ocular)	08
DLQI	
0 to 5 (no or small effect)	25
6 to 10 (moderate effect)	10
> 10 (very large effect)	5
Global assessment	
Absent/Mild	23
Moderate/Severe	17
Treatment	
No treatment [‡]	6
Topic	16
Systemic	14
Other	4

SD: standard deviation; F: female; M: male; DQLI: Dermatological Life Quality Index; * the same patient could have more than one subtype of rosácea; ‡ sunscreen included

Table 3 - Ocular surface parameters in rosacea patients and controls

	Control	Rosacea	p†
	<i>mean±sd(median)</i>	<i>mean±sd (median)</i>	
OSDI	6.01±9.40 (2.10)	26.30±22.10 (20.83)	<0.0001
Tear Meniscus (mm)	0.24±0.06 (0.23)	0.22±0.07 (0.22)	0.3382
NITBUT (seconds)	8.83±5.26 (7.26)	7.81±5.40 (5.93)	0.2282
Conjunctival Redness (grade 0-4)	1.23±0.64(1.20)	1.46±0.61 (1.30)	0.1064
Meibography	0 – 17.30% (9) 1 – 67.30% (35) 2 – 15.38% (8) 3 – 0% (0)	0 – 11.76% (4) 1 – 52.94% (18) 2 – 26.47% (9) 3 – 11.76% (4)	0,0258[‡]
Fluorescein Staining (grade 0-15)	0.47±0.64 (0.00)	0.74±1.07 (0.00)	0.4887
Invasive TBUT (seconds)	8.02±4.48 (7.00)	6.97±2.85 (7.00)	0.4709
Lisamine Staining (grade 0-9)	0.90±1.27 (0.00)	1.51±1.43 (1.00)	0.0152
Schirmer's Test (mm)	15.61±11.35 (15.00)	14.03±13.46 (9.50)	0.2438

†Mann Whitney Test; ‡ Chi-square Test; SD: Standard Deviation; OSDI: Ocular Surface Disease Index; NITBUT: Non-invasive Tear Breakup Time; TBUT: Tear Breakup Time

Table 4 - Ocular and eyelid border parameters of each rosacea subgroups

	Erythematous	Papulopustular	p†
Symptoms			
OSDI	39.76±24.55 (31.25)	18.52±15.77 (20.83)	0.0370
Tear volume			
Tear Meniscus Height	0.22±0.06 (0.21)	0.23±0.09 (0.23)	0.7252
Schirmer's Test	11.62±13.68 (6.50)	15.77±12.01 (12.0)	0.2104
Tear stability			
NITBUT	7.82±5.18 (6.69)	9.03±6.76 (5.90)	0.7923
Invasive TBUT	7.31±3.18 (7.0)	6.77±2.59 (7.0)	0.5959
Inflammation			
Conjunctival Redness	1.36±0.49 (1.30)	1.38±0.41 (1.40)	0.8603
Ocular Surface damage			
Fluorescein Staining	0.81±1.27 (0)	0.54±0.78 (0)	0.8006
Lisamine Staining	1.87±1.82 (1.0)	1.31±1.18 (1)	0.5858
Meibomian Gland dysfunction			
Meibography	0 – 11,76% (2)	0 – 15,38% (2)	0,2145 [‡]
	1 – 47,05% (8)	1 – 46,15% (6)	
	2 – 23,52% (4)	2 – 30,76% (4)	
	3 – 17,64% (3)	3 – 7,69% (1)	
Normal Secretion			p=1.000
Yes	0	0	
No	100%	100%	
Obstructed Glands			p=0.227
Yes	57.14%	27.27%	
No	42.86%	72.73%	
Granular Secretion			p=0.697
Yes	35.71%	45.45%	
No	64.29%	54.55%	
Pasty Secretion			p=0.043

Yes	14.29%	54.55%	
No	85.71%	45.45%	
Telangiectasias			P=0.209
Yes	85.71%	63.64%	
No	14.29%	36.36%	

†Mann Whitney Test; ☒ Chi-square Test; OSDI: Ocular Surface Disease Index; NITBUT: Non-invasive Tear Breakup Time; TBUT: Tear Breakup Time

Figures

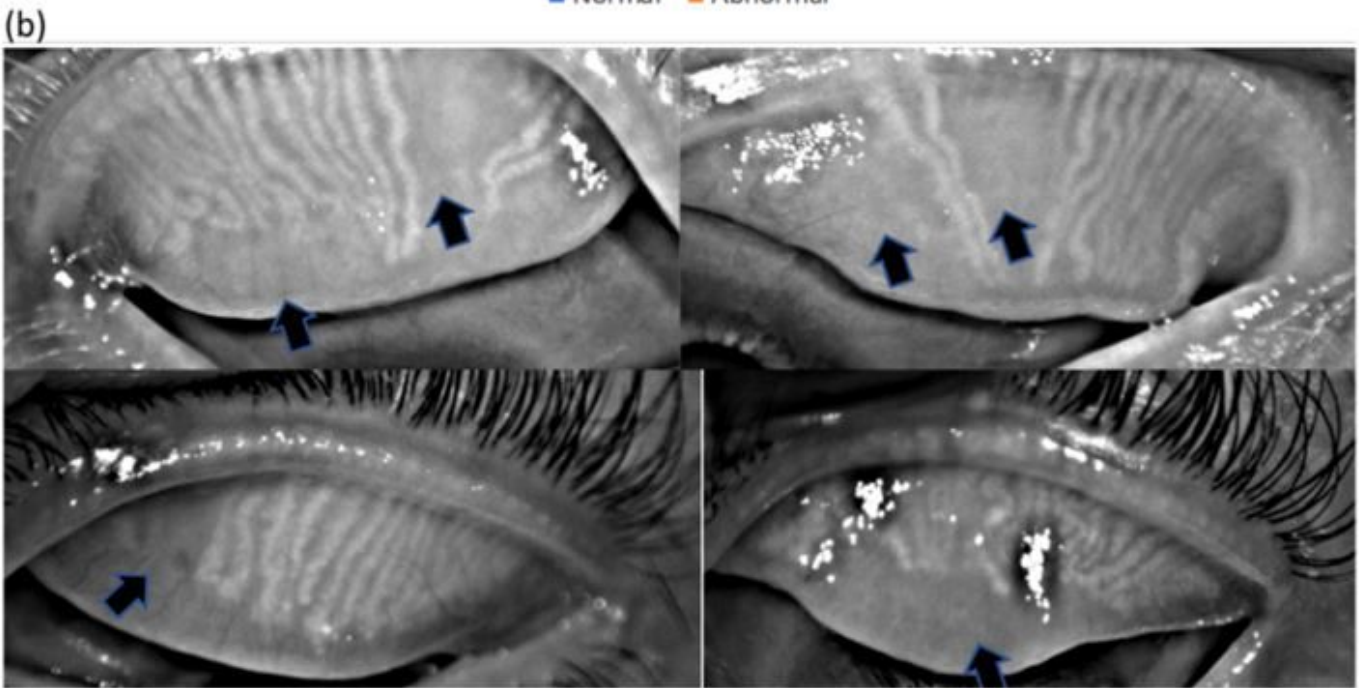
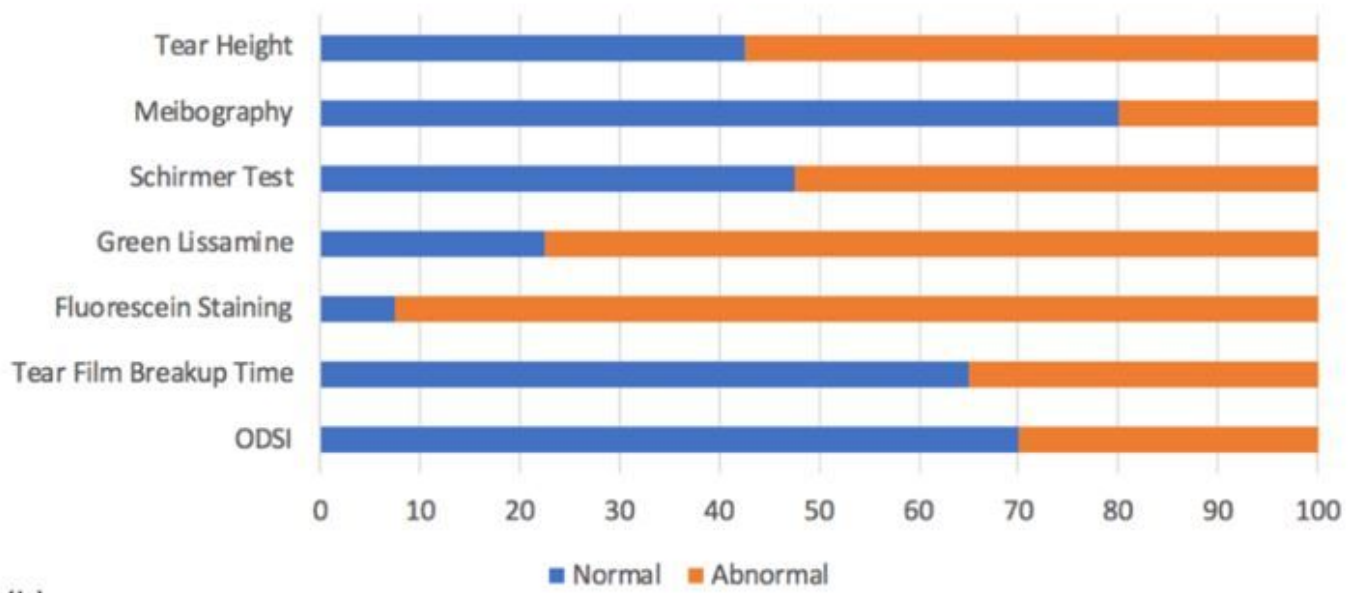


Figure 1

Ocular findings in Rosacea patients. (a) Frequency of ocular parameters (b) Meibomian Gland Dysfunction in Rosacea patients. Arrows showing glandular dropout.