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Original Article

Dry Eye and Meibomian Glands in Vitiligo

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Abstract

Objectives: To evaluate the aqueous and lipid tear film parameters and the meibomian glands with noncontact meibography in patients with vitiligo.

Materials and Methods: This case-control study was conducted in both eyes of 43 patients with vitiligo and 43 controls in Birjand, Iran. In addition to demographic information and skin disease characteristics, the Ocular Surface Disease Index (OSDI) questionnaire was completed for each patient. Then eye examinations including slit lamp, Schirmer test, Strip Meniscometry Tube (SMTube) and tear break up time (TBUT) were performed. The meibomian glands were also imaged using noncontact meibography system (SBM Sistemi, Italy). Finally, the data were analyzed by SPSS software version 22 at a significant level of less than 0.05.

Results: Patients had higher OSDI score than controls but it was not significant (10.90±13.03 vs. 5.57±6.85; p=0.07). There was a significant difference between the mean score of the Schirmer test in both eyes (OD: 8.07±5.47 vs. 17.37±6.52; OS: 7.60±5.00 vs. 17.30±6.44; p<0.001). The mean score of SMTube of both eyes was also significantly different (OD: 4.49±2.40 vs. 9.74±3.67; OS: 4.30±2.81 vs. 9.65±4.52; p<0.001). However, the mean TBUT of both eyes was not different between groups (OD: 9.14±3.17 vs. 10.12±2.08; p=0.27; OS: 9.16±3.30 vs. 10.05±2.10; p=0.25). Meibography by SBM Sistemi showed no significant difference in the atrophy rate of meibomian glands between groups (OD: 20.86±9.79 vs. 21.05±12.07; p=0.74; OS: 18.16±8.83 vs. 19.53±10.30; p=0.51).

Conclusion: Vitiligo is associated with a reduction in the production of aqueous tear film, but does not affect the structure and function of meibomain glands.

Keywords: Vitiligo, Dry eye, Meibomian glands

Introduction

Vitiligo is an acquired depigmentary disorder of the skin and mucous membranes affecting approximately 0.5–1% of individuals worldwide. It is characterized by well circumscribed, white macules and patches that may appear at any age. Vitiligo can be divided into two major subgroups: nonsegmental (NSV), which is more common and is often symmetrical, and segmental (SV), which occurs in a unilateral distribution (1). NSV is a multifactorial skin disorder with an immune-mediated melanocyte destructive mechanism. In contrast, SV is presumably a mosaic genetic skin disorder (2).

The main suggested hypotheses for the pathogenesis of vitiligo are the autoimmune theory, the neural theory, and the cytotoxic theory. The autoimmune theory plays a main role in the pathogenesis of NSV while the neural theory is more contributed in SV development. The autoimmune theory indicating autoimmune-mediating destruction of melanocytes is the most accepted mechanism in the pathogenesis of generalized vitiligo. The coexistence of vitiligo with several systemic and

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cutaneous autoimmune disease supports this theory (3). A cross-sectional study revealed that nearly 20% of the patients had at least one comorbid autoimmune disease. Thyroid disease and alopecia areata were the most commonly associated conditions in vitiligo (4). The association of vitiligo with Sjogren's syndrome, which includes dry eye as a diagnostic criterion, has been reported (5).

Melanocytes are present in other organs, such as the eyes, ears, heart, and nervous system. Accordingly, these organ systems in which melanocytes reside, may be involved in pigmentation disorders. Vitiligo has been associated with systemic disorders, such as Vogt-Koyanagi-Harada disease and Alezzandrini syndrome. Therefore, since uveal tract and retinal epithelium are rich of melanocytes, it is not surprising that vitiligo has ocular comorbidities (6).

Several studies have been conducted on the visual manifestations of vitiligo, which have reported findings such as retinal hypopigmentation, retinal pigment epithelial atrophy, and impaired retinal electrophysiologic function (7). However, few studies have investigated the ocular surface alterations in vitiligo showing tear film abnormalities, particularly in those with periocular involvement (8).

Dry eye disease is one of the most common ocular morbidities, with as many as 4.3 million Americans older than 65 years are affected to some degree. The impact of dry eye on quality of life was rated to be equivalent to unstable angina using utility assessments (9). The meibomian glands (MGs) are large sebaceous glands located in the tarsal plates of the eyelids secreting the lipid layer of tear film, which plays a key role in retarding tear evaporation (10). The assessment of MGs in various conditions such as dermatologic disorders has become a research topic because of recent introduction of the infrared technology for MGs imaging.

We hypothesize 'tear film paramaters worsen in vitiligo patients'. Accordingly, we evaluated the tear film parameters and MGs with noncontact meibography in vitiligo and compared these results with healthy individuals in Iranian population.

Material and methods:

Population and study design

This case-control study was conducted on both eyes of 43 patients with vitiligo and 43 controls in Birjand, Iran. The study protocol and examinations were reviewed and approved by the Ethics Committee of Birjand University of Medical Sciences (Ir.BUMS.REC.1396.302), and a written informed consent was obtained from all subjects. Patients with vitiligo diagnosed clinically by a dermatologist (ART) were included. Subjects with a systemic or ocular disease, recent use of drugs affecting the lacrimal unit, or current use of contact lenses were excluded.

In addition to demographic information and skin disease characteristics, the Ocular Surface Disease Index (OSDI) questionnaire was completed for each patient. Then eye examinations including slit lamp, tear break up time (TBUT), Schirmer test and Strip Meniscometry Tube (SMTube) were performed. None of the patients used topical artificial tear drops within 2 hours before the examinations. The meibomian glands were also imaged using BG-4M noncontact meibography system (SBM Sistemi, Turin, Italy). All of the above ophthalmic examinations were done by the same ophthalmologist (MN).

Ocular examinations

OSDI questionnaire includes 12 questions related to experience during the previous week which are subdivided into three groups including ocular symptoms, how these symptoms disturb visual function, and the ocular reaction to environmental triggers. The OSDI was measured on a scale of 0 to 100, with higher scores demonstrating greater disability (11).

TBUT (in second) is the time between the last blinking and the appearance of dry spot in stained tear film with fluorescein under a cobalt blue filter. This test was measured three times, and the mean of the measurements was considered as a final result. The lower TBUT indicates tear film instability. Ten seconds or greater is considered normal. According to the study protocol TBUT was performed initially, followed by SMTube and Schirmer test. A 30-min interval was applied between each examination to prevent disruption of the results.

Schirmer test is a strip that is placed at the junction of the middle and lateral thirds of the lower eyelid and the length of the tear wetting is measured in millimeters after 5 minutes (11). We applied Schirmer test I without topical anesthesia.

SMTube is noninvasive, promising new method that is expected to find application in the diagnosis and evaluation of the outcome of treatment of dry eye patients (12). SMTube had an acceptable sensitivity and specificity for assessing tear meniscus volume (13).

Meibography is the visualization of the glands through trans-illumination of the eyelid with infrared light. SBM Sistemi, detect the length and width of meibomian glands imaged by infrared meibography without requiring any input from the user. The images are then automatically classified. We performed the lower eyelid Meibography for the convenience and cooperation of patients (figure 1 and 2).

Statistical Analysis

The collected data were entered into SPSS 22 software and analyzed using appropriate statistical tests. According to the

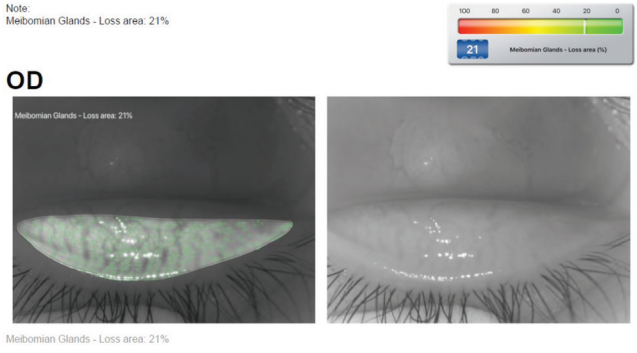

Figure 1. Meiboography imaging of right lower lid using SBM Sistemi in a normal control that shows minimal loss (21%) of mebomian glands

Shapiro-Wilk test, the normality distribution of the means was assessed. Then, the Mann-Whitney U test was used to compare the means in non-normal distributions instead of independent T-test in normalized one. In categorized variables chi-square and Fisher exact tests were used. The significance level was considered to be less than 0.05.

Results

The mean age in vitiligo group was 31.51 ± 13.30 years and in the control group was 33.23 ± 12.46 years. In the group of patients with vitiligo, 10 (23.3%) were men and 33 (76.7%) were women, and the control group consisted of 17 (39.5%) men and 26 (60.5%) women. The two groups were similar according to age and gender distribution (p-value$_{age}$=.47 and p-value$_{gender}$=.10; respectively). The mean duration of vitiligo was 7.26 ± 5.03 years, and the mean involvement area was 11.70 ± 9.49 percent of the total body surface area. There were 31 (72.1%) cases of facial involvement; three of them had bilateral upper and lower eyelids lesions.

The results of ocular examinations are outlined in table 1. Patients had higher OSDI score than controls but it was not significant (10.90±13.03 vs. 5.57±6.85; p=0.07). There was a significant difference between the mean score of the Schirmer test (OD: 8.07±5.47 vs. 17.37±6.52; OS: 7.60±5.00 vs. 17.30±6.44; p<0.001) and SMTube (OD: 4.49±2.40 vs. 9.74±3.67; OS: 4.30±2.81 vs. 9.65±4.52; p<0.001) in both eyes of vitiligo and control groups. The mean TBUT of both eyes was not different between groups (OD: 9.14±3.17 vs. 10.12±2.08; p=0.27; OS: 9.16±3.30 vs. 10.05±2.10; p=0.25).

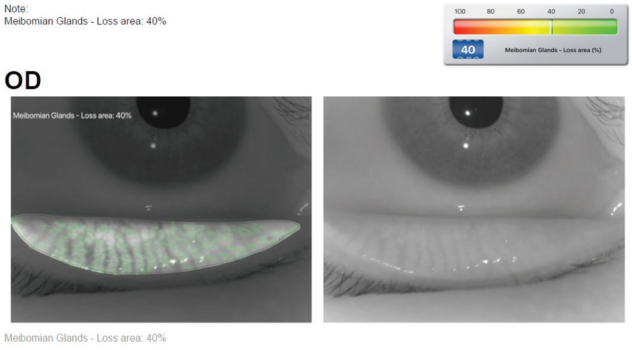

Figure 2. Meiboography imaging of right lower lid using SBM Sistemi that shows atrophy and dropout (40% loss) of mebomian glands in a patient with vitiligo

Meibography by SBM Sistemi also showed no significant difference in the atrophy rate of meibomian glands between groups (OD: 20.86±9.79 vs. 21.05±12.07; p=0.74; OS: 18.16±8.83 vs. 19.53±10.30; p=0.51).

Participants were categorized to have dry eye when they had OSDI equal or more than 13 and TBUT lower than 10. According to new version of dry eye definition, the cases of dry eye had no significant difference between patients and controls with the rate of 11.6% and 9.3% respectively (p=0.73). Finally, Pearson correlation test showed that facial involvement and disease duration had a non-significant correlation with OSDI score, Schirmer test, SMTube, TBUT, and MGs loss in studied patients (Table 2).

Discussion

The concurrence of vitiligo and ocular abnormalities has been explored by several studies. Some of them have been focused on ocular surface and dry eye evaluation in vitiligo. We employed Schirmer test and SMTube for assessing the aqueous tear film, and TBUT for evaluating the tear film stability. In addition, we studied the structure of mebomian glands using SBM Sistemi.

Dry eye diagnosis presents many challenges to the medical practitioner including no gold standard protocol for diagnosis, poor reliability for many common tests, and lack of well-defined cut-off values to distinguish disease from normal. The new definition of dry eye assigns an essential role for TBUT assessment, as well as the importance of visual impairment. According to new definition, dry eye disease is diagnosed by the combination of symptoms (OSDI>13) and unstable tear film (TBUT<10 sec) (14).

In this study, we observed that patients with vitiligo might have reduction in the production of aqueous tear film, however, there was no significant difference between patients and controls according to new version of dry eye definition. This result is reasonable regarding the cardinal role of OSDI and TBUT in

Table 1. Dry eye parameters and meibography results of the groups.

	Control group		Vitiligo group		p-value
	(mean ± SD)	R (min-max)	(mean ± SD)	R (min-max)	
OSDI score	10.90±13.03	52.08 (0-52.08)	5.57±6.85	29.17 (0-29.17)	0.07
Schirmer test (mm)	OD: 17.37±6.52 OS: 17.30±6.44	22 (5-27) 24 (6-30)	OD: 8.07±5.47 OS: 7.60±5.00	26 (0-26) 25 (0-25)	<0.001* <0.001*
SMTube (mm)	OD: 9.74±3.67 OS: 9.65±4.52	12 (3-15) 17 (3-20)	OD: 4.49±2.40 OS: 4.30±2.81	12 (1-13) 14 (2-16)	<0.001* <0.001*
TBUT (s)	OD: 10.12±2.08 OS: 10.05±2.10	11 (4-15) 11 (4-15)	OD: 9.14±3.17 OS: 9.16±3.30	13 (2-15) 13 (2-15)	0.27 0.25
MGs loss (%)	OD: 21.05±12.07 OS: 19.53±10.30	64 (4-68) 48 (3-51)	OD: 20.86±9.79 OS: 18.16±8.83	37 (4-41) 30 (4-34)	0.74 0.51#

* Mann-Whitney U test is significant at the level of 0.05
# independent T-test were used to compare mean of case and control groups

Table 2. Association of facial involvement and disease duration with OSDI score, Schirmer test, SMTube, TBUT, and MGs loss.

	OSDI score	Schirmer test (mm)		SMTube (mm)		TBUT (s)		MGs loss (%)	
		OD	OS	OD	OS	OD	OS	OD	OS
facial involvement	0.28 (0.07)	-0.26 (0.09)	-0.18 (0.25)	-0.13 (0.43)	-0.15 (0.34)	0.23 (0.14)	0.22 (0.16)	-0.19 (0.23)	-0.10 (0.53)
disease duration	-0.11 (0.48)	-0.10 (0.51)	-0.09 (0.56)	0.14 (0.37)	0.05 (0.73)	-0.03 (0.84)	0.003 (0.98)	-0.13 (0.42)	0.01 (0.94)

p-value for test of correlation is mentioned in parenthesis

new definition of dry eye, and lack of significant association of these parameters with vitiligo in our study.

The studies investigating tear film parameter in vitiligo have reported different and sometimes contradictory results. Karadag et al evaluated only Schirmer test as a tear film parameter in vitiligo and similarly showed a statistically significant difference between the vitiligo and control groups (15).

Gungor et al investigated TBUT and Schirmer test on 34 patients with different types of vitiligo. They found that the Schirmer test values in patients with vitiligo were insignificantly lower than those in the control subjects. However, the TBUT values of patients with vitiligo were significantly lower (16). A study by Dogan et al showed higher OSDI score, shorter TBUT, shorter Schirmer without statistical significance in vitiligo patients (17). Recently, Erdur et al. evaluated ocular surface and tear film parameters in vitiligo patients with and without periocular involvement and compared them with controls. They showed that patients with vitiligo had higher OSDI score, lower TBUT and higher tear osmolality. But there was no significant difference in Schirmer test and ocular surface staining between groups (18). Moreover, they concluded that ocular involvement was associated with higher tear osmolarity values. The results of these studies were inconsistent with our results. However, we also evaluated SMTube, a novel test for tear production assessment, which was significantly lower in vitiligo.

Palamar et al reported that OSDI score were higher while mean TBUT and Schirmer values were lower in vitiligo, the latter was similar to our results. To our knowledge, that was the only study investigating meibomian gland morphology in vitiligo patients. They showed significant differences in meibomian gland morphology in patients with vitiligo when compared with those without vitiligo. They evaluated upper and lower eyelid using infrared captures of a bio microscope (Topcon, SL-D701, Ijssel, The Netherlands). Their morphologic results was in contrast with our results (19). Notably, we examined only the lower eyelid and employed a different device (SBM Sistemi, Turin, Italy). The sample size in our study was doubled. The mean of meibomian gland atrophy in the eyes of our patients with vitiligo was more than the control group but that was not statistically significant.

Facial involvement in vitiligo might affect the eye, but this issue is more significant in patients with eyelid lesions. The association of periocular involvement with ophthalmic parameters was not assessed in this study due to small number of cases with eyelid lesions.

Study Limitations

The limitations of this study were a small sample size and lack of more comprehensive ocular surface investigations. Moreover, our meibography findings were limited to the lower eyelids. Despite all the limitations, we believe that this study has inspiring potential for future studies.

Conclusion

Vitiligo is associated with a reduction in the production of aqueous tear film, but does not affect the structure and function of meibomain glands.

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