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CLINICAL INVESTIGATION

Dry eye and tear film functions in patients with psoriasis

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Abstract
Purpose To evaluate dry eye symptoms, tear film function and ocular surface changes in patients with psoriasis.
Methods The Dry Eye Questionnaire and ophthalmic examination including the Schirmer test, tear break-up time, corneal fluorescein test, meibomian gland obstruction and conjunctival impression cytology were assessed in patients with chronic plaque psoriasis. Results were compared between 30 patients and 30 healthy controls.
Results The rate of positive responses in the Dry Eye Questionnaire and staining of corneal fluorescein test were significantly higher in the patients ($P = 0.030$) than in the controls ($P = 0.012$). The tear break-up time in patients was significantly lower than in the controls ($P < 0.001$). However, there were no differences in the Schirmer test and meibomian gland function between the patients and controls. In the impression cytology analysis, more cell alteration and decreased goblet cell density were observed in the patients ($P < 0.001$) compared with those obtained from controls ($P = 0.003$).
Conclusions The dry eye symptom was more common in patients with psoriasis. In addition, the patients showed a higher tear film instability and significant degeneration on the ocular surface when compared with the normal controls.

Keywords Dry eye · Impression cytology · Psoriasis · Tear film

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Introduction

Psoriasis is a chronic inflammatory skin disease that results from excessive proliferation of the underlying epidermis; however, the etiology of this disease is still unknown [1]. The overall prevalence of psoriasis is about 2 % of the world population [2]. Psoriasis is usually limited to the skin but is also accompanied by systemic inflammation, so is often associated with multiple comorbidities, such as debilitating arthritis, myocardial infarction and the metabolic syndrome [3].

This disease shows wide variation in severity and in distribution of skin lesions with multiple extracutaneous manifestations. Although vision-threatening ophthalmic complications are very rare, it is reported that ocular effects occur in about 10 % of psoriasis patients [4–6]. In addition, ophthalmic complications of psoriasis are numerous and have a non-specific nature, such as blepharitis, conjunctivitis, keratitis and xerosis [7]. Therefore, ophthalmic involvement in psoriasis remains clinically underappreciated. Information on the manifestations of these effects is limited and varies considerably between ophthalmic and dermatological studies [5, 6]. In addition, the impact of psoriasis on the status of the ocular surface and the associated alterations still needs to be clarified.

The purpose of this study was to investigate dry eye symptoms and other ophthalmic complications in patients

with psoriasis and to analyze the effect of psoriasis on the ocular surface relative to healthy controls.

Methods

We examined a series of patients with chronic plaque psoriasis in the Department of Dermatology of Chuncheon Sacred Heart Hospital from September 2011 through March 2012. While nummular-type and large plaque-type psoriasis were included in this study, other types of psoriasis, such as guttate type, erythrodermic and generalized pustular psoriasis and palmoplantar pustulosis, were not. Patients with ocular or medical problems other than psoriasis were excluded. Patients who wore contact lenses were also excluded. Thirty-five patients were recruited, but one was excluded because of the use of glaucoma eyedrops and four refused the ophthalmic examination. Therefore, this study consisted of 30 patients (a total of 60 eyes) with chronic plaque psoriasis. The 60 eyes of 30 healthy volunteers served as the controls.

The diagnosis of psoriasis was made by a single dermatologist (YH). The severity of the psoriasis of each patient was determined based on the Psoriasis Area and Severity Index (PASI) [2]. All patients were questioned for disease duration, joint involvement, and psoriasis treatment modalities received currently and during the previous 5 years. Healthy, age-matched volunteers without any ophthalmic or skin disease served as the control group. The study protocol was approved by the Institutional Review Board of Hallym Medical Center, and informed consent was obtained from all study participants.

A Dry-Eye Questionnaire (DEQ), determination of the tear-film break-up time, fluorescein staining of the ocular surface, meibomian gland grading, Schirmer tests with anesthesia and conjunctival impression cytology were performed in sequence for each patient during their hospital visit.

Dry eye symptoms were evaluated using the DEQ, which included six questions pertaining to dry eye symptoms [8, 9] (see Appendix). When a participant indicated the presence of a symptom, she or he was asked to indicate whether the symptom was experienced rarely, sometimes, often or all the time. "Positive dry eye symptom" was defined as having one or more of the symptoms often or all the time.

Slit-lamp examinations were also performed by an experienced ophthalmologist (JWL) blinded to the DEQ and Schirmer test results. The BUT was defined as the time taken from blink until the appearance of the first randomly distributed dark spots or streaks within the fluorescein-enhanced tear film. The BUT was measured three times for each eye and the average was recorded. Fluorescein staining of the cornea was scored as 0 (no staining), 1 (mild staining limited to <1/3 of the cornea), 2 (moderate staining of <1/2 of the cornea) or 3 (severe staining occupying one half or more of the cornea) [10]. Meibomian gland obstructions were graded 0 (no obstruction with clear meibomian), 1 (plugging with translucent serous secretion when compressing the lid margin), 2 (plugging with viscous or waxy white secretion when compressing the lid margin) or 3 (plugging with no secretion when compressing the lid margin). Meibomian gland dysfunction (MGD) was diagnosed as the presence of gland orifice plugging (grade >1) [11]. Whenever the results of each eye were different, the higher degree of grade was recorded for analysis. The Schirmer test with the instillation of topical anesthetics was performed using a pre-calibrated dry filter strip (Color Bar; EagleVision, Inc., Memphis, TN, USA) that was placed temporally in each lower fornix. The average distance at which the paper was wet in both eyes after 5 min was recorded as the Schirmer value of the subject.

The impression cytology specimens were obtained after administration of topical anesthesia. Strips of cellulose acetate filter paper (GSWP01300, Millipore Corp., Bedford, MA, USA) were applied on the upper temporal bulbar conjunctiva adjacent to the corneal limbus, pressed gently by a glass rod and then removed. The filter was immediately collected onto gelatin-coated glass slides. The specimens were then fixed with formaldehyde, stained with periodic acid-Schiff, and dehydrated in ascending grades of ethanol and xylol. The quantitative studies of conjunctival goblet cells and squamous metaplasia of conjunctival epithelial cells were conducted by taking photographs using a calibrated grid under a light microscope at a magnification of $\times$400. We imaged 5 overlapping areas of each sample selected at random and averaged the outcomes for a single sample score. The goblet cell densities were reported as cells per square millimeter with standard deviations. The specimens were also assigned a grade of conjunctival epithelial squamous metaplasia according to Nelson's grading scheme [12]. In accordance with this method, the presence and density of goblet cells, morphological changes in the nucleus, the nucleus-cytoplasma ratio and metachromatic changes in the cytoplasm were considered for a grade from 0 to 3. All specimens were evaluated by the same pathologist (SHH), who was masked as to whether the specimens came from patients or controls.

Statistical analysis was performed using a commercially available statistical software package (SPSS for Windows, version 12.0; SPSS, Chicago, IL, USA). Categorical analysis was conducted using the independent t test, Mann–Whitney U test, Chi-square test or Fisher's exact test as appropriate. Data were analyzed via repeated-measures analysis of variance with a Bonferroni correction. The level

of statistical significance was set at 0.05 (2-sided) in all statistical tests.

Results

The mean age (±SD) of the patients' group was 34.3 ± 22.0 (range, 23–74 years) and of the control group 37.8 ± 13.9 (range, 28–60 years), ($P = 0.815$, independent t test). There were 16 men and 14 women in the patient group and 14 men and 16 women in the control group ($P = 0.567$, Fisher's exact test).

The mean duration of the disease was 7.8 ± 7.3 years (range 1–20 years). The mean PASI score was 5.8 ± 3.4 (range, 1–13.2), and the grade of psoriasis based on PASI was mild in 19 patients, moderate in 7 patients and severe in 4 patients. No patient showed joint involvement. Sixteen of the 30 patients had received prior ultraviolet phototherapy, and 10 of the 30 patients had been medicated with oral cyclosporine. Four of the 30 patient used topical ointment for the skin lesions. No patient had facial or eyelid psoriasis plaques.

Eleven (36.6 %) of the 30 patients reported experiencing positive dry eye symptoms (at least one of the symptoms often or all the times) in the DEQ, and 3 (10 %) of the 30 controls reported experiencing positive dry eye symptoms. The rate of difference was significant ($P = 0.030$, Chi-square test). The total score for the DEQ was 3.2 ± 2.2 (range 0–7) in the patients and 1.6 ± 1.5 (range 0–4) in the controls ($P = 0.01$, Mann–Whitney U test).

In the slit-lamp examination, the mean BUT was shorter in the patients (7.4 s) than in the controls (10.2 s), and this difference was statistically significant ($P = 0.001$, Mann–Whitney U test). In the corneal fluorescein test, the mean score was 0.5 ± 0.5 in the patients and 0.2 ± 0.4 in the controls ($P = 0.008$, Mann–Whitney U test). In the anterior segment analyses, disorders such as pterygium, pingecula, marginal corneal infiltrates or ulceration were not observed in either the patient or control groups. No patient displayed a cell reaction on the anterior chamber or vitreous.

MGD was observed in 14 (46.6 %) of the 30 patients and 12 (40 %) of the 30 controls. The rate of MGD was not different ($P = 0.807$, Chi-square test). The average values determined from the Schirmer test were 9.1 ± 5.8 mm for patients and 11.5 ± 5.5 mm for controls. No significant difference was evident in the Schirmer test ($P = 0.263$, Mann–Whitney U test). Schirmer test results of <5 mm (pathologic Schirmer) were not observed in the controls. However, two (6.6 %) of the patients showed pathologic Schirmer test results. The rates of pathologic Schirmer results were not different ($P = 0.246$, Chi-square test). A comparison between the two groups is provided in Table 1.

Table 1 The Dry Eye Questionnaire, tear film and meibomian gland characteristics of patients with psoriasis and controls

	Patients ($n = 30$)	Controls ($n = 30$)	P value[a]
Positive dry eye symptom on questionnaire	11 (36.6 %)	3 (10 %)	0.030
Tear break-up time (s)	7.4 ± 3.1	10.2 ± 4.0	<0.001
Fluorescein test (scores)	0.5 ± 0.5	0.2 ± 0.4	0.008
Schirmer test (mm/5 min)	9.1 ± 5.8	11.5 ± 5.5	0.263
Meibomian gland dysfunction	14 (46 %)	12 (40 %)	0.807

[a] Mann–Whitney U test for continuous variables and the Chi-square test for categorical variables

According to epithelial and goblet cell morphologic features, 4 (13.3 %) showed grade 1, 6 (20 %) showed grade 2 and 20 (66.6 %) showed grade 3 in patient group. In the control group, 8 (26.6 %) showed grade 0, 12 (40 %) showed grade 1, 7 (23.3 %) showed grade 2 and 3 (10 %) showed grade 3.

There was a statistically significant difference between the patients and controls with regard to the distribution of impression cytology grades ($P < 0.001$, Chi-square test). The goblet cell density (cells/mm^2) was 109 ± 120 in patients, which was significantly lower than in the controls (390 ± 204) ($P = 0.003$, independent t test). A comparison of cytology between the two groups is provided in Table 2.

There was no significant difference in DEQ, tear film tests and impression cytology according to PASI score, duration of disease, prior phototherapy, cyclosporine medication or use of topical ointment ($P > 0.05$).

Discussion

The prevalence of dry eyes judged by using subjective symptoms was reported to vary widely from 15 to 70 % in population-based studies [8–10, 13]. There is no previous report presenting the incidence of dry eye with dry eye symptom questionnaires in patients with psoriasis. In this study, we positively defined the dry eye symptom as the presence of one or more dry eye symptoms occurring often or all the time. Although there is no gold standard among dry eye tests, the DEQ used in this study is reported to be reliable and reproducible [9, 13, 14]. In addition, although dry eye disease (DED) has a heterogenic nature, for comparison purposes, we controlled the typical factors associated with DED including age, gender and ethnicity [15, 16]. In this study, the dry eye symptom was determined to be about 36 % in psoriasis patients, significantly higher than the 10 % in age-matched healthy controls. These results revealed a high incidence of dry eye in psoriasis patients.

Table 2 Comparison of the conjunctival impression cytology grades and goblet cell density between patient with psoriasis and the controls

	Patients ($n = 30$)	Controls ($n = 30$)	P value[a]
Grade based on epithelial and goblet cell morphologic features (grade, 0:1:2:3)	0:4:6:20	8:12:7:3	<0.001
Goblet cell density (cells/mm^2)	109 ± 120	390 ± 204	0.003

[a] Independent t test for continuous variables and the Chi-square test for categorical variables

The Schirmer value of psoriasis in our study did not differ between the patients and the controls. These findings are consistent with previous reports [14, 17–19]. Gudmudsen et al. [19] report 18.75 % of psoriasis patients showed pathologic Schirmer results. This is a higher incidence than the 6.6 % of our results. Because they did not present any detailed information about their patients, such as mean age or severity of psoriasis, direct comparison of the results is difficult. However, we think the reason for the lower incidence of pathologic Schirmer results in this study would be the different characteristics of the study population.

The Schirmer test primarily measures aqueous tear secretions and might be useful for aqueous deficient dry eye. Thus, we believe that tear secretion was not mainly affected by the presence of psoriasis. However, the decrease in the tear film BUT was more significant in psoriasis patients. The BUT is generally used to assess tear film stability, and studies show that a shorter BUT, as observed in the patients, can lead to ocular surface damage. The higher rate of corneal punctuate erosion in the fluorescein test for patients with psoriasis supports this hypothesis.

The incidence of meibomian gland dysfunction, on the other hand, was not different in the psoriasis patients. This finding was not in agreement with the results of a previous report. Zengin et al. [18] found that patients with psoriasis had higher plugging and thickness indices, but normal volumes of meibomian gland secretions. In addition, they propose that there was a mechanical block through the meibomian duct, which lead to tear film instability in psoriasis. The method of classification of the meibomian gland status in the present study was different from theirs, and changes in the study population and examiner could also have an effect on the grade of meibomian gland dysfunction. However, we did not find a significant MGD in the psoriasis patients when compared to the controls. Although MGD may cause tear film instability and quantification of MGD might be subjective, we believe that the results of this study suggest another mechanism, and MGD does not seem to contribute to tear film instability in psoriasis patients [11, 20].

It is interesting that decreased goblet cell density and a high incidence of squamous metaplastic changes were observed in psoriasis patients on the impression cytology. Goblet cell density reflects the overall health of the ocular surface [21, 22]. This abnormality in epithelial differentiation consists of a continuous spectrum in which the normal secretory conjunctival mucosa gradually develops into a non-secretory keratinized epithelium. As a result, the tear film becomes unstable secondary to a reduction in the mucin layer of the tear film [23]. Considering the association between impression cytology and tear function, mucin layer dysfunction would be important in the ocular findings of psoriasis [24, 25]. However, we did not perform immunohistochemical studies of the mucin distribution in the conjunctival cells obtained by impression cytology or measure the variation in mucin concentrations in the tear fluid. Further studies are needed to determine the precise mechanism behind the complex pathophysiology related to mucin production in psoriasis patients.

Psoriasis is a chronic inflammatory disease with a complex pathophysiology and a multigenic background. The pathogenesis of both dry eye and psoriasis is not fully understood. In the pathogenesis of dry eye, T cells infiltrate the ocular surface and secrete inflammatory cytokines and chemokines, causing squamous metaplasia of ocular surface epithelial cells and a decrease in goblet cell differentiation [26]. Similar to dry eye, T-cells in the keratinocytes in psoriatic skin were shown to induce immune-mediated inflammation, one of the main causes of psoriasis [27, 28]. Since keratinocytes in the skin form the initiation area of psoriasis pathogenesis, the conjunctiva might be the primary sites for ocular involvement [29, 30]. Moreover, it is reported that in psoriasis, the ocular histopathology is similar to the cutaneous changes with less parakeratosis [29]. Another possible mechanism explaining the tear film instability in psoriasis would be L-arginine deficiency. The L-arginine concentration is shown to be significantly reduced in psoriatic skin [31]. L-Arginine is a major component contributing to the synthesis of the beta-defensins induced under dry eye conditions [32]. Moreover, L-arginine deficiency in systemic disease is significantly associated with dry eye syndrome [33]. The association between psoriasis and dry eye may be accompanied by L-arginine deficiency and increased b-defensin production. Thus, we think that there is a common denominator between dry eye and psoriasis. These connections might induce dry eye symptoms and ocular surface changes in psoriasis patients.

There are some limitations to this study. First, the DEQ may also be reflective of other ocular surface diseases, including MGD and conjunctivitis. Thus, it is not specific

for DED, and its incidence may be overestimated. Moreover, some dry eye symptoms might not be covered by the DEQ. Therefore, more specific criteria for diagnosing the development of dry eye symptoms are required, and the newly revised questionnaire consisting of ocular symptoms, visual function and environmental triggers may be helpful [34]. Second, only a relatively small number of patients was used in this study. This small sample size might limit the statistical power in detecting differences in the factors that may influence the outcomes and did not allow statistics using multiple categorizations of patients. The relatively minor degree of psoriasis in the population was also a limitation of the study. Thus, larger population-based studies are necessary. Finally, we could not define the detailed pathogenesis of the tear film changes in psoriasis patients. Further studies will be required to clarify this issue.

The ocular effects of psoriasis are often neglected or underappreciated, and the link between a patient's ophthalmic symptoms and their underlying psoriasis may be missed by physicians. Based on the results of this study, clinicians should remain mindful of the association between psoriasis and dry eyes.

In summary, we observed dry eye symptoms and ocular surface differences in psoriasis patients when compared to healthy controls. This study indicates that dry eye in patients with psoriasis is common, and the tear film was relatively unstable with ocular surface damage when compared with normal controls.

Appendix

See Table 3.

Table 3 The Dry Eye Questionnaire (DEQ)

1. Do your eyes feel dry?
2. Do you feel gritty or sandy sensation in your eyes?
3. Do your eyes ever have a burning sensation?
4. Do your eyes ever feel sticky?
5. Do your eyes ever feel watery or tearing?
6. Are your eyes ever red?

Allowed responses to the questions included "none," "rarely," "sometimes" and "often or all the time." Positive dry eye symptom was defined as having one or more dry eye symptoms often or all the time.

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