DOI: 10.4274/tjo.galenos.2022.98752
Turk J Ophthalmol 2022;52:374-378

Original Article

The Effect of Prolactinoma on Tear Film Function

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Abstract

Objectives: To compare dry eye parameters in prolactinoma patients and healthy controls and evaluate their correlation with prolactin (PRL) levels and the duration of hyperprolactinemia.

Materials and Methods: Consecutive patients with prolactinoma and healthy controls were included in the study. Schirmer, tear break-up time (TBUT), tear osmolarity values, and ocular surface disease index (OSDI) scores were evaluated for each patient. Follow-up time and total duration of hyperprolactinemia were recorded for prolactinoma patients.

Results: The study included 39 eyes of 39 patients with prolactinoma and 39 eyes of 39 age- and gender-matched healthy controls. Prolactinoma patients showed lower Schirmer (14.1±8.4 vs. 24.8±8.9 mm; p<0.001) and TBUT values (7.0±3.2 vs. 11.6±2.6 s; p<0.001) and higher OSDI scores (20.6±16.6 vs. 5.8±2.4; p<0.001) compared to the healthy controls. While the mean osmolarity of the prolactinoma patients was 301.6±8.3 mOsm/L, it was 297.7±12.5 mOsm/L for the healthy controls (p=0.07). The duration of hyperprolactinemia in prolactinoma patients showed a negative correlation with Schirmer (r=-0.395; p=0.013) and TBUT values (r=-0.377; p=0.018) and a positive correlation with OSDI scores (r=0.337; p=0.036).

Conclusion: Prolactinoma patients had significantly lower Schirmer and TBUT levels and higher OSDI scores compared to the healthy controls, but no significant difference in tear osmolarity. The effect of high PRL levels on tear film function was duration-dependent.

Keywords: Prolactinoma, dry eye, Schirmer, tear osmolarity, tear break-up time

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Received: 24.08.2021 **Accepted:** 22.01.2022

Cite this article as: Doğan C, Güleser ÜY, Kılıçarslan O, Mergen B, Açbay Ö, İskeleli G. The Effect of Prolactinoma on Tear Film Function. Turk J Ophthalmol 2022;52:374-378

Introduction

Prolactinoma is a pituitary adenoma which originates from prolactin (PRL)-producing cells of the pituitary gland. It occurs more frequently in middle-aged women, especially between the second and fifth decades. The female-to-male ratio of the disease was reported to be 10:1, and its prevalence is 100 per million cases.[1,2] With its benign nature, adenoma does not spread to local tissues or distant organs. Prolactinoma shows its effects in the body via hormonal differences or local pressure on the adjacent structures. Hyperprolactinemia disrupts reproductive hormone production and causes different signs and symptoms in both male and female patients. Amenorrhea, oligomenorrhea, galactorrhea, and hirsutism are among the most commonly observed symptoms in female patients. Erectile dysfunction, loss of libido, and gynecomastia are commonly observed in male patients. If prolactinoma remains undiagnosed, it can cause pressure signs such as headache, diplopia, and visual field loss.[1,2,3]

Dry eye disease (DED) is one of the most common causes of ocular irritation in adults.[4] Rheumatologic pathologies such as rheumatoid arthritis, systemic lupus erythematosus, and Sjögren's syndrome may accompany DED or it may present as a primary ocular problem without any accompanying disease. The most frequent symptoms are common ocular irritation symptoms like burning, stinging, lacrimation, and red eyes. Schirmer's test, tear break-up time (TBUT), tear osmolarity, slit-lamp examination, and ocular surface disease index (OSDI) scores can be utilized in the diagnosis and grading of DED.[4,5]

DED is observed more frequently with older age, possibly due to a decrease in gonadal hormone levels during menopause.[6] Hyperprolactinemia inhibits gonadotropin-releasing hormone (GnRH) and follicle stimulating hormone (FSH), which in turn may cause a decrease in gonadal hormone levels. Androgen hormones are strong stimulating factors for meibomian gland function and important in the regulation of ocular surface inflammation.[7] Recent studies have suggested that androgen deficiency is a potential contributor to dry eye.[7,8] Previous in vivo studies showed the presence of prolactin-like molecules and PRL receptors in acinar cells and some interstitial cells of the lacrimal gland.[9] In one study, drug-induced hyperprolactinemia was related to a change in the collagenous structures of the lacrimal gland in rats.[10] Additionally, serum PRL levels have been shown to have strong negative correlations with tear film function in women undergoing hormone replacement therapy.[11] This growing body of evidence may indicate a possible role of hyperprolactinemia in tear film functions.

Our study aimed to compare dry eye parameters (Schirmer's test, TBUT, tear osmolarity, and OSDI scores) in prolactinoma patients to those of healthy controls and evaluate their correlation with PRL levels and duration of hyperprolactinemia.

Materials and Methods

The study included consecutive patients diagnosed with prolactinoma and healthy controls. All patients underwent a complete ophthalmological examination to exclude any coexisting ocular pathology other than DED that might affect the results of the tests. Only the right eyes of the patients were included in the study. Age, gender, and the follow-up duration since the diagnosis of prolactinoma were recorded. Patients who had any systemic diseases other than prolactinoma or were using any systemic or topical medication that might affect tear functions were excluded. Smokers and individuals with prolonged screen exposure (more than one hour per day) were excluded from the study. The study was conducted according to the Declaration of Helsinki and was approved by the local ethics committee. Informed consent was obtained from the patients before the examination.

Prolactinoma patients were included in the study regardless of their serum PRL levels on their screening day for the study. Therefore, both controlled and uncontrolled prolactinoma patients were included. Patients who had normal serum PRL levels during follow-up were considered controlled prolactinoma patients, whereas patients who had hyperprolactinemia on the day of screening and for at least 6 months in total during follow-up despite oral cabergoline therapy were regarded as uncontrolled prolactinoma patients. Hyperprolactinemia was defined as a PRL level >25 ng/mL in female patients and >20 ng/mL in male patients. The total duration of previous hyperprolactinemia (in months) was calculated from the patients' medical records.

Schirmer's test, TBUT values, and OSDI scores were recorded for each patient. Schirmer's test was performed without topical anesthesia at the same hour of the day for all patients. TBUT was performed after staining with a fluorescein strip at least 30 minutes after Schirmer's test. OSDI scores were calculated according to the patients' responses to the questionnaire. Tear osmolarity was measured with the TearLab Osmolarity System (TearLab, San Diego, CA, USA). The mean value of two measurements obtained at the same time was accepted as the tear osmolarity value. Tears were collected from the inferior lateral meniscus without any contact with the conjunctiva.

Statistical Analysis

Data distributions were evaluated for normality using the Shapiro-Wilk test. Student's t-test was used to compare the means of the groups with normally distributed data and the Mann-Whitney U test was used to compare those without normal distribution. For the correlation analysis, Spearman's correlation test was used. P values below 0.05 were accepted as statistically significant. SPSS version 21.0 (IBM Corp, Armonk, NY, USA) was used for all statistical analyses.

Results

Thirty-nine eyes of 39 patients with prolactinoma and 39 eyes of 39 healthy controls were included in the study. The mean age was 39.6±13.5 years for the prolactinoma patients and 35.2±6.5 years for the control group (p=0.08). The female-to-male ratios of the groups were 24:15 and 23:16, respectively (p=0.817). Twelve patients (31%) had controlled and 27 patients (69%) had uncontrolled PRL levels. Twenty-six patients received oral cabergoline throughout follow-up.

The mean Schirmer value was 14.1±8.4 mm in the prolactinoma group and 24.8±8.9 mm in the control group (p<0.001). The prolactinoma and control groups' mean TBUT values were 7.0±3.2 s and 11.6±2.6 s (p<0.001) and their mean OSDI scores were 20.6±16.6 and 5.8±2.4, respectively (p<0.001). The results are shown in Table 1.

The patients' mean duration of hyperprolactinemia was 24.6±27.5 months (range: 3-117) and the mean serum PRL level was 28±32.4 ng/mL (range: 0.86-150) at the time of examination.

The correlation analysis results of the prolactinoma patients are shown in Table 2. The duration of hyperprolactinemia in prolactinoma patients showed a negative correlation with Schirmer (r=-0.395; p=0.013) and TBUT values (r=-0.377; p=0.018) and a positive correlation with OSDI scores (r=0.337; p=0.036).

Discussion

Prolactinoma is a pituitary adenoma that causes high serum PRL levels. Although the effect of androgen hormones on the lacrimal gland and tear function has been investigated extensively, the effect of elevated serum PRL on tear function in humans has not been evaluated yet. In this study, we showed that prolactinoma patients had significantly lower Schirmer and TBUT values and higher OSDI scores in comparison to the healthy controls. While the duration of hyperprolactinemia in these patients showed a negative correlation with Schirmer and TBUT values, it was positively correlated with OSDI scores.

High PRL levels cause a decrease in the levels of GnRH and FSH, which in turn might cause a decrease in the estrogen and androgen levels. Although androgens have been shown to increase the synthesis and secretion of lipids from the meibomian glands, estrogens have been shown to decrease lipid production.[12] The effect of sex steroids seems more complex. Azcarate et al.[7] showed that patients with decreased androgen levels after the development of andropause had high dry eye syndrome scores and lower TBUT values. Antiandrogen therapy was also linked to meibomian gland dysfunction and lipid tear deficiency.[8] Additionally, topical androgen therapies were also suggested for dry eye patients to provide symptomatic relief.[13] In addition to androgens, estrogens have been suggested to play an important role in the regulation of tear film function because of evidence that the frequency of dry eye syndrome increases dramatically in the postmenopausal period and estrogen replacement therapy improves tear film function.[14,15,16,17] Despite the conflicting results regarding the effect of estrogen replacement therapy on tear film function, a recent meta-analysis of 7 different studies showed that estrogen replacement therapy significantly improved Schirmer test results without any significant effect on TBUT.[14] However, the studies included in the meta-analysis had small sample sizes and even the treatment approach was

Table 1. Comparison of dry eye parameters in prolactinoma patients and healthy controls

	Prolactinoma (n=39)	Control (n=39)	p value
Schirmer (mm)	14.1±8.4	24.8±8.9	<0.001
TBUT (s)	7.0±3.2	11.6±2.6	<0.001
OSDI	20.6±16.6	5.8±2.4	<0.001
Osmolarity (mOsm/L)	301.6±8.3	297.7±12.5	0.07

TBUT: Tear break-up time, OSDI: Ocular surface disease index

Table 2. Correlation of PRL levels and duration of hyperprolactinemia duration with dry eye parameters

		Age	Schirmer	TBUT	Osm	OSDI	PRL	HPL Duration
Age		1.000						
	p	.						
Schirmer	r	-0.127	1.000					
	p	0.440	.					
TBUT	r	0.137	0.473**	1.000				
	p	0.405	0.002	.				
Osm	r	0.129	-0.145	-0.076	1.000			
	p	0.447	0.392	0.655	.			
OSDI	r	-0.090	-0.076	-0.574**	0.125	1.000		
	p	0.584	0.646	0.000	0.462	.		
PRL	r	0.096	0.301	-0.016	-0.078	0.230	1.000	
	p	0.561	0.063	0.925	0.648	0.160	.	
HPL duration	r	-0.058	-0.395*	-0.377*	0.097	0.337*	-0.121	1.000
	p	0.728	0.013	0.018	0.567	0.036	0.464	.

r: Correlation coefficient TBUT: Tear break-up time, Osm: Osmolarity, OSDI: Ocular surface disease index, PRL: Prolactin, HPL: Hyperprolactinemia
*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).

heterogeneous. Thus, further randomized controlled clinical trials are needed to clarify the effect of hormone replacement therapy on tear film function. All of these supporting findings may explain why prolactinoma caused dry eye syndrome.

Numerous studies showed the presence of PRL receptors on the acinar cells of the lacrimal gland and one study also showed the presence of PRL in the tear film.[9,18] A study on a PRL receptor knockout model showed that hyperprolactinemia caused a hyperfemale morphology, suggesting a role of PRL in dry eye syndromes.[19] Hyperprolactinemia in a mouse model was also shown to cause alterations in acinar cells (cellular disorganization, changes in their volume, and altered spacing between the acini) and the amount of collagen in the lacrimal gland in female mice.[10] Mathers et al.[11] showed that serum PRL levels had strong negative correlations with tear film functions in women under hormone replacement therapy. All of these findings support that PRL might have a direct regulatory negative effect on tear film function in the pathogenesis of dry eye syndrome in the prolactinoma patients in our study. Increased levels of serum PRL might have a negative effect on the production of the aqueous part of the tear film, while decreased sex steroids might have a negative effect on meibomian gland function, leading to a decrease in the Schirmer and TBUT values. However, the presence of PRL receptors in the human lacrimal gland and the presence of PRL in the human tear film should be studied extensively to support this hypothesis.

Although we showed decreased TBUT and Schirmer values and increased OSDI scores in prolactinoma patients, we observed no change in tear osmolarity levels in prolactinoma patients. This interesting finding might be explained as the effect of PRL not being related to the inflammatory status of the tear film. Instead, PRL might adversely impact only the production of the aqueous and lipid layers of the tear film, thereby affecting Schirmer and TBUT values without any effect on tear osmolarity, because tear osmolarity is related mostly to the release of the inflammatory cytokines, especially in patients with Sjögren's syndrome.[20]

After observing lower Schirmer and TBUT values and higher OSDI scores in prolactinoma patients, we further analyzed the duration of high serum PRL levels to evaluate its correlation with dry eye status. Our findings showed that the duration of hyperprolactinemia correlated negatively with Schirmer and TBUT values and positively with OSDI scores. Therefore, we concluded that the effect of high PRL levels was duration-dependent. Thus, patients with prolactinoma should be monitored for dry eye-related symptoms.

Study Limitations

Limitations of our study include the absence of serum estrogen and androgen levels of the patients, because the complex effect of prolactinoma on tear film function can be better analyzed with the consideration of sex steroid levels. Another limitation of the study is the exclusion of the patients' fellow eyes. We included only one eye to avoid the double organ bias. However, examination of both eyes for tear osmolarity difference between two eyes might have given important data related to the dry eye status of the patients. Future studies may also examine the tear osmolarity difference in prolactinoma patients.

Conclusion

In conclusion, here we showed that prolactinoma patients had lower Schirmer and TBUT levels and higher OSDI scores compared to the healthy controls, with no significant difference in tear osmolarity. The duration of high serum PRL levels showed a negative correlation with Schirmer and TBUT values and a positive correlation with OSDI scores. Thus, our study suggests that high serum PRL levels might disturb tear film functions in a duration-dependent manner and that patients with prolactinoma should also be questioned about dry eye-related symptoms. However, these findings should be improved with further studies on the effect of PRL on the lacrimal gland and tear film function.

Ethics

Ethics Committee Approval: İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Clinical Research Ethics Committee.

Informed Consent: Obtianed.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: O.K., Concept: C.D., Ü.Y.G., Design: C.D., Ü.Y.G., Data Collection or Processing: O.K., B.M., Analysis or Interpretation: B.M., Literature Search: O.K., B.M., Ü.Y.G., Writing: C.D., Ü.Y.G., O.K., B.M., Ö.A., G.İ.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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