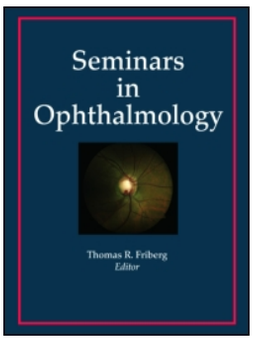

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Association between Blepharoptosis and Pterygium in Korea: A Population-Based Study during 2010-2012

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ABSTRACT

Purpose: To investigate possible correlations between blepharoptosis and pterygium in a nationally representative sample of the Korean population.

Methods: This population-based, cross-sectional study was comprised of 3,685 males and 4,792 females (≥ 19 years of age) participating in the fifth annual Korea National Health and Nutrition Examination Survey (KNHANES) from 2010 to 2012. The enrolled subjects underwent interviews, clinical examinations, and laboratory tests. Statistical tests were used to compare the prevalence of blepharoptosis, according to pterygium subtypes or pterygium existence. Multiple logistic regression analyses were also used to find the associations of blepharoptosis with pterygium.

Results: Pterygium was present in 10.3% of males and 9.8% of females. The odds ratios (ORs) of pterygium in Korean males significantly decreased as the severity of blepharoptosis increased (p for trend = 0.0252). Using three models in multivariate analyses, males with blepharoptosis had an OR (95% confidence interval, (CI)) of 0.643 (0.435 ~ 0.951) for pterygium compared with males with no blepharoptosis, after adjusting for age, body mass index, smoking status, alcohol consumption, physical activity, serum vitamin D levels, diabetes mellitus, metabolic syndrome, high blood pressure, and stress intolerance. There was no significant association between blepharoptosis and females.

Conclusions: The association between blepharoptosis and pterygium in the Korean population showed a gender difference. Epidemiologic evidence only showed a negative correlation between blepharoptosis and pterygium in Korean males. Further studies are needed, therefore, to examine the sex difference in the pathogenesis of pterygium.

Keywords: Pterygium, blepharoptosis, population-based, gender difference, epidemiology

INTRODUCTION

Pterygium is a common, benign, wing-shaped, fibrovascular growth from the bulbar conjunctiva onto the cornea.[1] Pterygium occurs in multiethnic populations, with a widely varying prevalence (1.2–23.4%).[2–4] Histologically, it is characterized by elastotic degeneration of altered basal cells and hyperproliferative vessels.[5,6] Many previous studies have suggested that the pathogenesis of pterygium involves a complex disease with genetic, environmental, infective, and immunological components.[7–9] Notably,

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a wide variety of proinflammatory cytokines and angiogenic and fibrogenic growth factors have been implicated in pterygium.[6] Because some of these factors are affected by exposure to ultraviolet-B (UVB) light, evidence from multiple sources has suggested that populations with high exposure to sunlight are at an increased risk of pterygium.[10] Although the pathogenesis of pterygium is still not fully known, it is thought to be caused by reactive oxygen species (ROS) formation after exposure to UV light, low humidity, or dust.[7–11]

Blepharoptosis is a common ophthalmic disorder characterized by an abnormally low-lying upper eyelid margin < 2 mm above the midpoint of the pupil or > 2.0 mm lower than the contralateral eyelid margin.[12] It is generally considered to develop from an aponeurotic dehiscence or aponeurotic defect itself of the levator palpebrae superioris muscle.[13] This might be caused by involutional changes around the upper eyelid and orbit, including degenerative fatty changes in the aponeurosis and fat pad of the upper eyelid.[14] In severe cases, blepharoptosis symptoms can cause impairment of the superior visual field and central vision. It is possible that blepharoptosis subjects have low upper eyelid height and may have been exposed to decreased sun exposure or UVB light, when compared with subjects with a normal upper eyelid height.

If UVB light (e.g., sun exposure) is a possible risk factor for pterygium, there is the possibility of a different pterygium morbidity according to the severity of blepharoptosis; the greater the blepharoptosis severity, the less chance of sun exposure. To the best of our knowledge, no study has reported the association between blepharoptosis and pterygium in the Korean population. In the present study, we evaluated the pterygium morbidity according to the severity of blepharoptosis. This study was part of the Korea National Health Survey, an ongoing nationally representative and population-based cross-sectional survey conducted in different provinces in Korea.

METHODS AND MATERIALS

Study Sample

This study was a cross-sectional analysis of the fifth annual Korea National Health and Nutrition Examination Survey (KNHANES-V). We used data obtained from a representative sampling between 2010 and 2012, gathered by the Division of Chronic Disease Surveillance, a division of the Korea Centers for Disease Control and Prevention (KCDC). Sampling units were based on household unit data obtained from the 2010 National Census Registry, including details related to geographical area, sex, and age. A stratified multistage probability sampling method was used with a rolling sampling model. Information was collected from Korean households representing the noninstitutionalized civilian population. The survey was comprised of a health interview, health examination, and nutrition survey administered to a representative sampling of the Korean population. Data were collected by household interviews and direct, standardized, physical examinations conducted in mobile examination centers. The interviewers were not provided with any information regarding specific participants before conducting the interviews, and all participants completed written consent forms prior to enrollment. Institutional Review Board (IRB)/Ethics Committee approval for the study was obtained from The Catholic University of Korea in accordance with the Declaration of Helsinki.

Of the 29,345 participants initially sampled, 7,424 participants <19 years of age and 13,334 participants with missing data were excluded. Participants with missing data didn't have ophthalmologic results including the upper eyelid height measurements. A final total of 8,477 participants (3,685 males and 4,792 females) were included in the final analyses. All participants provided written consent forms prior to enrollment. This survey was reviewed and approved by the Institutional Review Board of the KCDC.

MEASUREMENTS

Questionnaires were used to collect data on the respondents' demographic characteristics, smoking history, alcohol consumption, exercise, residential district (urban or rural), spouse, occupation, educational status, income, and food and nutritional intake. Smoking status was categorized into two groups, involving current smokers and nonsmokers. The amount of pure alcohol consumed (g/day) was calculated using the average number of alcoholic beverages consumed by the respondents and the frequency of alcohol consumption. Regular exercise was defined as strenuous physical activity performed for at least 20 minutes at a time, at least three times a week. Respondents who drank more than 30 g/day of alcohol were classified as heavy drinkers. The residential area was defined as urban or rural, with urban areas including both large and small cities. The education level was classified as high if the respondent had completed a post-university education. The 24-hour dietary recall method was used to collect data on food items consumed by the participants. Energy and fat intake were calculated based on the consumption of each food item.

OPHTHALMIC EXAMINATIONS

A slit-lamp examination (model BQ-900; Haag-Streit AG, Koeniz, Switzerland) was performed by an ophthalmologist to determine the presence of disease and its subtypes in the anterior segment of the eye. Pterygium was defined as a radially oriented fibrovascular lesion crossing the nasal or temporal limbus. An atrophic pterygium was defined as a pterygium that allowed clear discernment of the underlying episcleral vessels. A flesh pterygium was defined as a thick pterygium that did not allow visualization of the episcleral vessels. All other pterygia that were not defined by these two categories were listed as intermediate. The recurrence was listed as no recurrence, one episode of recurrence, and more than two episodes of recurrence. Pterygium subjects were defined as those with one pterygium in at least one eye. If a patient had pterygia in both eyes, we evaluated the more severe eye.

THE MEASUREMENTS OF UPPER EYELID HEIGHT

The MRD1 was measured from the central upper lid margin to the pupillary light reflex on the cornea.[15,16] The value of the MRD1 were measured and categorized into 4 groups 1) ≥ 3.0 mm(millimeters); 2) 2.0–2.9 mm; 3) 1.0–1.9 mm; 4) < 1.0 mm, and blepharoptosis was defined as the presentation of a marginal reflex distance 1 (MRD1) of < 2 mm[15-17] in either eye. During measuring MRD1, the subjects have to be positioned at the physician's eye level. The subjects were asked to look straight ahead and focus on a distant target. The physician shone a penlight into the subject's eye, and recorded the distance from the corneal light reflex to the upper lid margin in mm. All lid positions of subjects were examined by specially trained physicians who had been conducting routine ophthalmic examinations for over 3 years. The quality of the ophthalmic survey was proved by the Epidemiologic Survey Committee of the Korean Ophthalmologic Society. The differential diagnosis of blepharoptosis was made with special attention to pseudoptosis associated eyebrow ptosis and dermatochalasis.

STATISTICAL ANALYSES

Statistical analyses were performed using SAS software, version 9.2 (SAS Institute, Cary, NC, USA) and SUDAAN, version 10.1 (Research Triangle Institute, Research Triangle Park, NC, USA). This was a software package that incorporated sample weights and adjusted analyses for the complex sample design of the survey. Survey sample weights were used in all analyses to produce estimates that were representative of the noninstitutionalized civilian Korean population.

The demographic characteristics of the study participants were expressed as either the mean ± standard error (SE) or numbers and prevalence ± SE, as appropriate, for total participants. The survey weights were used to obtain the SEs of prevalence. Differences between clinically diagnosed pterygium with controls for all participants' demographic, socioeconomic, and anthropometric characteristics were analyzed using the Student's t-test or chi-square test, as appropriate, using the SURVEYMEANS or SURVEYFREQ procedures in SAS to reflect the study weights, respectively.

The prevalence of blepharoptosis, according to pterygium subtypes or pterygium existence, was compared using the Chi-square test. Multivariate adjusted logistic regression analyses were conducted to examine the odds ratio (OR) and 95% confidence interval (CI) for the possible associations between pterygium and blepharoptosis after adjusting for age in Model 1. Model 2 was adjusted for age, body mass index (BMI), smoking history, alcohol consumption and physical activity. Model 3 was then adjusted for all variables in Model 2 plus serum vitamin D levels, diabetes, metabolic syndromes, hypertension, and stress. We used metabolic syndrome and its components as major variables in Model 3, because previous report found that metabolic syndrome and its components associated with representative ophthalmologic disease such as cataract.[18] For logistic regression analyses, the SURVEYLOGISTIC procedure in SAS was used. All reported p-values were two-tailed, and a value of $p < 0.05$ was considered to be statistically significant.

RESULTS

Baseline Characteristics (Table 1)

The baseline characteristics of participants according to the presence of pterygium for both sexes are shown in Table 1. Among eligible participants, 381 (10.3%) of 3,685 males and 468 (9.8%) of 4,792 females reported having pterygium. The mean age of males with pterygium was 61.9 ± 0.8 years, while that of males without pterygium was 54.3 ± 0.2 years ($p < 0.0001$). The mean age of females with pterygium was 65.7 ± 0.7 years, while that of females without pterygium was 55.9 ± 0.2 years ($p < 0.0001$). Table 1 shows the results of univariate analyses of the associations between pterygium and demographic characteristics, lifestyle, and medical factors among males and females. Based on univariate analyses, factors associated with a composite outcome of pterygium were less smoking, a rural residence, less employment, less education, less income, more cataracts, more hypertension, less stress, older age, a less BMI,

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TABLE 1. Clinical characteristics of the study participants according to the presence or absence of pterygium.

	Male (n = 3,685)			Female (n = 4,792)		
	Pterygium			Pterygium		
	No n = 3,304	Yes n = 381	*p-value	No n = 4,324	Yes n = 468	*p-value
Current smoker, %	33.9 (1.2)	31.9 (2.9)	0.0097	41.4 (0.4)	3.4 (1.1)	0.549
Heavy drinker, %	19.4 (0.9)	16.6 (2.8)	0.358	1.0 (0.2)	0.3 (0.2)	0.041
Exercise (yes), %	23.2 (1.0)	25.2 (2.8)	0.4654	18.6 (0.8)	20.1 (2.3)	0.4887
Place (rural), %	23.5 (2.5)	43.1 (4.6)	<0.0001	23.2 (2.3)	46.2 (4.7)	<0.0001
Spouse, %	92.1 (0.7)	92.0 (1.7)	0.9776	77.1 (2.8)	57.1 (2.8)	<0.0001
Occupation, %	81.0 (0.9)	70.8 (2.9)	<0.0001	51.0 (1.0)	51.2 (3.1)	0.9611
Education, % of ≥12 years	64.8 (1.3)	40.4 (3.4)	<0.0001	45.7 (1.3)	10.9 (2.0)	<0.0001
Income, % of lowest Q1	17.5 (0.8)	34.3 (3.0)	<0.0001	23.7 (0.9)	41.8 (2.8)	<0.0001
Cataract	38.5 (1.5)	55.2 (3.9)	<0.0001	39.3 (1.4)	69.5 (2.9)	<0.0001
Blepharoptosis	11.7 (0.9)	12.9 (2.1)	0.544	10.7 (0.9)	22.0 (2.7)	<0.0001
Metabolic syndrome, %	36.3 (1.1)	38.0 (3.5)	0.624	35.7 (0.9)	80.8 (3.0)	<0.0001
Diabetes, %	15.1 (0.8)	14.6 (2.4)	0.8599	10.8 (0.6)	14.9 (2.0)	0.0344
Hypertension, %	42.6 (1.1)	52.8 (3.2)	0.002	36.5 (0.9)	51.4 (3.1)	<0.0001
Stress perception, %	22.0 (0.9)	15.6 (2.6)	0.0347	27.2 (0.9)	28.3 (2.4)	0.6757
Recurrence						-
No	100.0 (0.0)	-		100.0 (0.0)	-	
1 episode	-	70.3 (2.9)		-	72.1 (2.3)	
≥2 episodes	-	29.7 (2.9)		-	27.9 (2.3)	
Transparancy						-
No	100.0 (0.0)	-		100.0 (0.0)	-	
Atrophic	-	53.7 (3.9)		-	56.7 (3.6)	
Intermediate	-	37.6 (3.6)		-	34.4 (3.0)	
Fleshy	-	8.7 (1.9)		-	8.9 (2.1)	
Age, years	54.3 ± 0.2	61.9 ± 0.8	<0.0001	55.9 ± 0.2	65.7 ± 0.7	<0.0001
BMI, kg/m^2	24.1 ± 0.1	23.2 ± 0.2	<0.0001	23.9 ± 0.1	24.4 ± 0.2	0.0447
WC, cm	85.4 ± 0.2	83.9 ± 0.6	0.0207	80.5 ± 0.2	83.1 ± 0.5	<0.0001
Vitamin D	19.4 ± 0.2	20.6 ± 0.5	0.0103	17.3 ± 0.2	19.0 ± 0.4	<0.0001
Length, mm	-	1.9 ± 0.2	-	-	1.9 ± 0.1	-

*p-values were calculated using the chi-square test for categorical variables or the independent t-test for continuous variables.

Data are presented as mean ± standard error (SE) for continuous varibales or % SE for categorical variables. BMI, body mass index; n, number; WC, waist circumstance.

a less waist circumference (WC), and greater serum vitamin D levels in males. Females with pterygium showed less drinking, a rural residence, less education, less income, more diabetes, more hypertension, older age, a larger BMI, a larger WC, and greater serum vitamin D levels compared to females without pterygium.

The Prevalence of Blepharoptosis according to the Presence of Pterygium (Figure 1, Table 2)

Figure 1 shows the blepharoptosis prevalence rate according to pterygium subtypes. There was a different prevalence pattern between males and females. Males with atrophic and fleshy types of pterygium had less blepharoptosis comorbidity than males with no pterygium. Otherwise, females with all three types of pterygium had more blepharoptosis comorbidity than females with no pterygium. Both males and females with intermediate type pterygium had significantly more blepharoptosis comorbidity than the other types and those with no pterygium (p = 0.0226, <0.0001, respectively). We also examined the blepharoptosis prevalence for subjects with or without pterygium. Table 2 shows that males 40 ~ 49 and 50 ~ 59 years of age had a significantly higher prevalence of blepharoptosis if they did not have pterygium. However, there was no significant association between blepharoptosis prevalence and pterygium in Korean females.

The Association of Pterygium according to the Severity of Blepharoptosis (Figure 2, Table 3)

Figure 2 shows the ORs of pterygium according to the severity of blepharoptosis. The ORs of pterygium in Korean males significantly increased as the severity of blepharoptosis decreased (p for trend = 0.0252); however, the ORs of pterygium were not associated with blepharoptosis in females (p for trend = 0.8504). Table 3 shows the ORs (95% CIs) of pterygium in relation to blepharoptosis. In males, after adjustment for age (Model 1), subjects with blepharoptosis (MRD1 < 2)

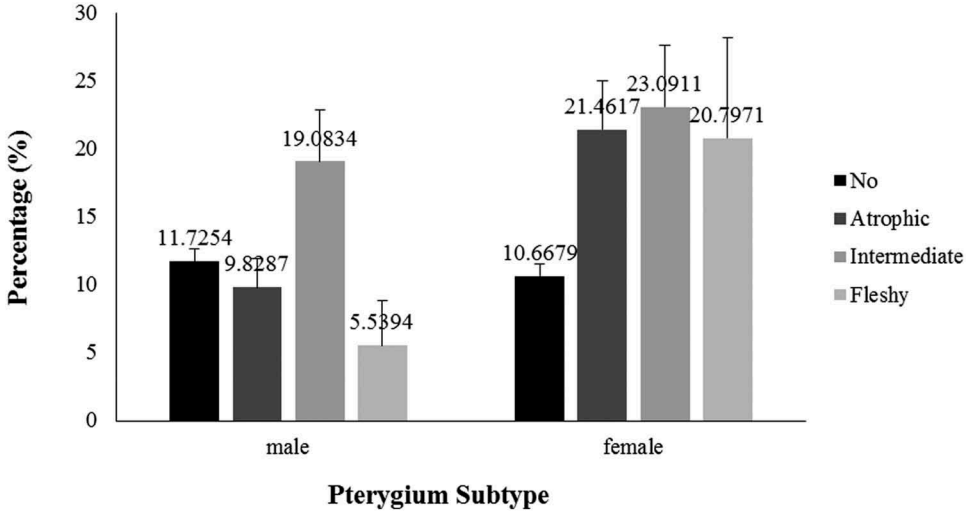

FIGURE 1. Blepharoptosis prevalence (%) according to pterygium subtypes. Pterygium subtypes included none, atrophic, intermediate and fleshy.

TABLE 2. The percentage (%) of blepharoptosis according to the existence of pterygium.

	Male			Female		
Age	No	Yes	p-value	No	Yes	p-value
40–49	6.2 (1.0)	1.1 (1.1)	0.0488*	1.8 (0.5)	7.1 (6.7)	0.1427
50–59	9.4 (1.3)	1.2 (0.9)	0.0005*	7.4 (1.1)	7.7 (3.3)	0.9263
60–69	17.6 (1.9)	14.4 (3.5)	0.4038	15.5 (1.7)	18.8 (4.3)	0.4208
≥70	29.1 (2.4)	30.4 (5.4)	0.8086	31.5 (2.4)	35.0 (4.8)	0.4459

* The p-value was calculated using the chi-square test.

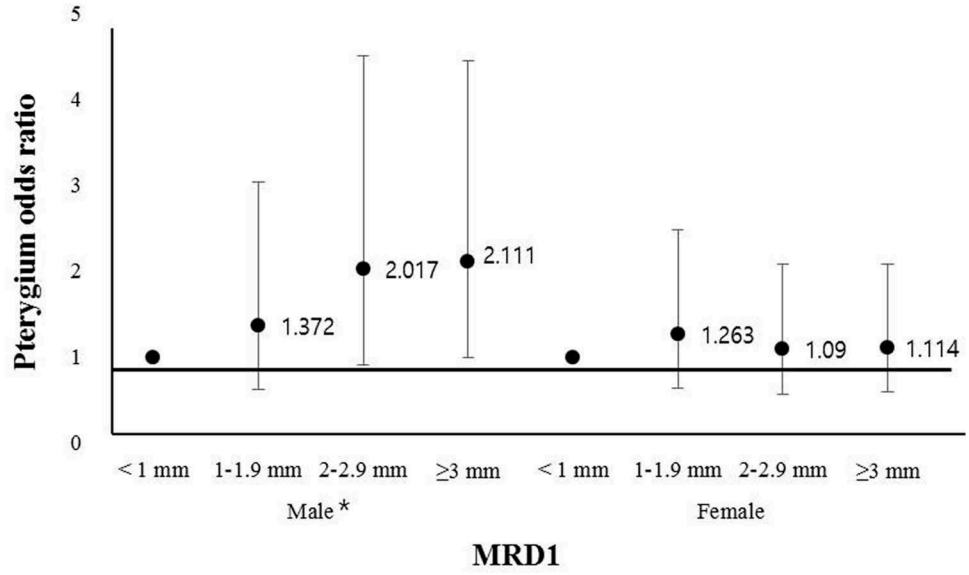

FIGURE 2. The pterygium odds ratio according to bleaphroptosis severity (blepharoptosis grades; marginal reflex distance 1 (MRD1) < 1 mm, 1–1.9 mm, 2–2.9 mm, and≥ 3 mm) (*P for trend is obtained using general lineal model, P for trend for males = 0.0252, P fore trend for females = 0.8904).

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TABLE 3. ORs (95% CIs) of having ptreygium in relation to blepharoptosis.

	Male		Female	
	OR (95%, CI)	p-value	OR (95%, CI)	p-value
Model 1	0.674 (0.473,0.959)	0.0283*	1.139 (0.839,1.547)	0.4042
Model 2	0.719 (0.499,1.035)	0.0762	1.122 (0.827,1.523)	0.46
Model 3	0.643 (0.435,0.951)	0.0271*	1.197 (0.845,1.3696)	0.312

ORs, odds ratio; CIs, confidence intervals

*The p-value was calculated using hierarchical multivariate logistic regression analyses.

†Model 1 was adjusted for age.

‡Model 2 was adjusted for age, body mass index (BMI), smoking, alcohol consumption, and exercise.

§Model 3 was adjusted for age, BMI, smoking, alcohol consumption, exercise, vitamin D levels, diabetes, metabolic syndromes, hypertension, and stress.

had a significant OR (95% CI) of 0.674 (0.473 ~ 0.959) for pterygium (p = 0.0283). After a further adjustment for BMI, smoking status, alcohol consumption, physical activity, serum vitamin D levels, diabetes mellitus, metabolic syndromes, high blood pressure, and stress intolerance (Model 3), males with blepharoptosis had an OR (95% CI) of 0.643 (0.435 ~ 0.951) for pterygium, and showing that males with blepharoptosis were at significantly less risk for pterygium (p = 0.0271). The risk of pterygium was not significantly associated with blepharoptosis in females, irrespective of adjustments for confounding variables.

DISCUSSION

To the best of our knowledge, this is the first large population-based study to investigate possible correlations between blepharoptosis and pterygium. We performed a cross-sectional study to investigate and compare the prevalence and risk factors of pterygium in representative Korean population. The prevalence of pterygium was 10.02% in subjects older than 19 years of age. When analyzed with combined data, blepharoptosis was significantly associated with pterygium in males and blepharoptosis comorbidity significantly reduced the risk of pterygium in Korean males. This association was independent of possible confounding factors such as age, BMI, smoking, exercise, serum vitamin D levels, diabetes, metabolic syndromes, hypertension, and stress. However, there was no significant negative association between blepharoptosis and pterygium in females.

Blepharoptosis is a common eyelid disorder characterized by an abnormally low-lying upper eyelid margin less than 2.0 mm above corneal center or greater than 2.0 mm lower than the contralateral eyelid margin, and is one of the most common upper eyelid disorders.[12] The symptoms are accompanied by impairment of the superior visual field and central vision in severe cases, and except for congenital type blepharoptosis, they worsen during aging process.[13,14] Although blepharoptosis is generally characterized with an MRD1 < 4 ~ 5mm in Western populations, there are no accurate definitions or available data for the prevalence of blepharoptosis among Asian or Korean populations. Moreover, there are many more differences in facial and orbit anatomy among Asians when compared with Western populations. Therefore, we defined blepharoptosis as an MRD < 2 mm as suggested by other reports written by Shirado and Yoon et al.[15,16] The development of any pterygium is likely to be the result of a multifactorial process, including UV-B light irradiation, local and systemic conditions, as well as psychological aspects.[3,4,6] The present study showed that pterygium was correlated with some periocular conditions such as blepharoptosis, which increase our understanding of the etiology and development of pterygium. It is because people with more severe blepharoptosis may have less UV-B light irradiation.

UV-induced free radicals, through a photochemical reaction, are believed to be important in the development of pterygium.[19–21] Although it is still unclear, ROS generated by exposure to UV light has been reported to trigger release of factors for conjunctival disease such as pterygium, and there are many studies on the association between the oxidative stress effect and antioxidant defense mechanisms.[22,23] Consistent with this possibility, Kormanovski et al. reported that a primary pterygium group showed an increase in nitric oxide (NO) and total antioxidant status (TAS) levels, and a decrease in the levels of all antioxidant enzymes compared with the control group. They also found that there was a significant decrease in the levels of TAS and antioxidant enzymes in the recurrent pterygium group.[22] These results strongly supported the idea that oxidative stress plays an important role in the pathogenesis and recurrence of pterygium. In the present study, we also suggested a possible correlation of blepharoptosis and sun exposure, which can further explain the deleterious effects of UVB light and oxidative stress.

We found sex differences in the correlation between blepharoptosis and pterygium. Previous reports also reported differences in pterygium development between females and males.[24–28] Differences in UVB radiation

during occupational exposure may be a significant environmental factor. In our study, there was a difference between males and females in the prevalence of blepharoptosis according to the subtype of pterygium (Figure 2). In males, atrophic and fleshy subtype pterygium showed less blepharoptosis comorbidity, but in the female population, all three subtypes of pterygium showed more blepharoptosis comorbidity than the subjects without pterygium. Although the mechanism underlying these differences was not clear, it may be related to sexual or hormonal differences. In the female population, not only UVB exposure but also other hormonal factors including estrogen protection may inhibit oxidative stress to influence the development of pterygium.[29]

The clinical implications of these results suggested that, for Korean males, blepharoptosis comorbidity may have a protective effect against pterygium development. This possibility is consistent with the idea that UVB-induced free radicals play a role in the development of pterygium. Notably, these results were found only in the male population and not in the female population. A strength of this study was its large sample size, with standardized ocular assessments by ophthalmologists and comprehensive assessments of associated factors. However, the cross-sectional analyses limited the ability to explain causality, and the assessment of UVB exposure and hormonal changes were relatively crude when compared with common limitations of other population-based studies.

In conclusion, this study showed that the risk of pterygium was negatively associated with blepharoptosis, irrespective of adjustments for confounding factors in males. Our findings regarding the association between pterygium and blepharoptosis may allow physicians to counsel patients about possible modifiable factors. Further prospective studies are necessary to understand more fully the relationships between blepharoptosis, pterygium, sex differences, oxidative stress, and hormonal changes.

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COMPETING INTERESTS

The authors have declared that no competing interests exist.

AUTHOR CONTRIBUTIONS

JP, KH designed and analyzed the study and drafted all versions of the manuscript. KN advised on design, analysis, and reviewed successive drafts of the manuscript. HK, SY, and WC designed study and reviewed successive drafts of the manuscript. KH designed some of the study materials, contributed to analysis and measured big data analysis.

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