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Ocular Factors Relevant to Keratoepitheliopathy in Glaucoma Patients With and Without Diabetes Mellitus

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Purpose: To examine the effect of diabetes mellitus on the keratoepitheliopathy in glaucoma patients with and without diabetes mellitus who were treated with anti-glaucoma eye drops.

Methods: The presence and severity of keratoepitheliopathy was investigated in the eyes of 36 glaucoma patients with diabetes mellitus and 47 nondiabetic patients who had glaucoma. All the patients had used anti-glaucoma eye drops. The ocular factors examined were the status of the lipid layer of the tear fluid assessed by a specular reflection video recording system, the tear volume assessed by the Schirmer test, and the tear film stability assessed by tear break-up time (BUT).

Results: The incidence of superficial punctate keratitis (SPK) was 36.1% in the diabetic patients with glaucoma and 27.7% in the nondiabetic patients with glaucoma. Serious cases of SPK were seen only in the diabetic patients with glaucoma. The uniformity of the tear lipid layer, results of the Schirmer test, and the tear BUT in the diabetic patients with glaucoma were similar to those in the nondiabetic patients with glaucoma.

Conclusion: In glaucoma patients who use anti-glaucoma eye drops, the effects of diabetes mellitus on the keratoepitheliopathy and other ocular factors are not significant. However, we must consider the serious cases of keratoepitheliopathy in these patients. **Jpn J Ophthalmol 2003;47:287–290**

Key Words: Anti-glaucoma eye drops, diabetes mellitus, keratoepitheliopathy.

Introduction

Keratoepitheliopathy is often seen in patients with diabetes mellitus and also in glaucoma patients treated with anti-glaucoma eye drops. The keratoepitheliopathy in patients who have diabetes mellitus and use anti-glaucoma eye drops is occasionally severe and difficult to cure. However, because the patterns of keratoepitheliopathy are similar in slit-lamp examinations in these two groups, it is not clear whether it is the diabetes mellitus or the use of anti-glaucoma eye drops that contributes more to the inducement and worsening of the keratoepitheliopathy.

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia associated with microvascular and/or macrovascular complications. Diabetic patients may develop not only diabetic retinopathy but also a keratoepitheliopathy such as superficial punctate keratitis (SPK), recurrent corneal erosion, or persistent epithelial defects. Diabetic keratoepitheliopathy is induced by quantitative and qualitative abnormalities in the tear secretion and a decrease of corneal sensitivity.[1]

Various types of eye drops that function differently have been developed, and several kinds may be used in combination. Corneal damage caused by eye drop toxicity is also often seen, especially damage caused by an adverse reaction to anti-glaucoma eye drops. SPK, corneal anesthesia (decrease in corneal sensitivity), a decrease of tear break-up time (BUT), decrease in tear volume determined by the Schirmer test, and nonuniformity in the tear lipid layer have been reported as adverse reactions to anti-glaucoma eye drops.[2] The mechanism for the development of keratoepitheliopathy as an adverse reaction to anti-glaucoma eye drops appears to be similar to that in diabetic keratoepitheliopathy.

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The incidence of keratoepitheliopathy is higher in diabetic patients treated with anti-glaucoma eye drops than in diabetic patients who do not have glaucoma and do not use eye drops.[3] The contribution of anti-glaucoma eye drops to the development of keratoepitheliopathy is significant in diabetic patients. However, there has been no study that compared the incidence of keratoepitheliopathy and the ocular factors in glaucoma patients with and without diabetes mellitus who use anti-glaucoma eye drops.

The aim of this study was to determine whether diabetes mellitus increases the incidence of and worsens the keratoepitheliopathy seen in glaucoma patients treated with anti-glaucoma eye drops. We evaluated the differences in ocular factors that contributed to the keratoepitheliopathy in glaucoma patients with and without diabetes mellitus who were treated with anti-glaucoma eye drops.

Materials and Methods

We studied 36 corneas of 19 glaucoma patients who were being treated with anti-glaucoma eye drops. These patients also had diabetes mellitus (8 men and 11 women) and were patients at the Nadogaya Hospital in September and October 2001 (the diabetic group). Their mean ($\pm$ SD) age was 67.0 $\pm$ 9.8 years with a range of 49–83 years. There were 12 eyes with primary open angle glaucoma (POAG) and 24 eyes with normal tension glaucoma (NTG). The duration of the glaucoma could not be determined.

The average number of types of anti-glaucoma eye drops used was 1.6 $\pm$ 0.9 (range, 1–4), but the duration of the use of the eye drops was not known. The anti-glaucoma eye drops prescribed were timolol, carteolol, nipradilol, latanoprost, dorzolamide, and dipivefrine. The number of types of anti-glaucoma eye drops used by each patient was as follows: one in 23 eyes (63.9%), two in 8 eyes (22.2%), three in 3 eyes (8.3%), and four in 2 eyes (5.6%). The mean duration of diabetes mellitus was 12.6 $\pm$ 8.4 years (range, 6 months to 30 years). Fourteen eyes did not have diabetic retinopathy, and 22 had nonproliferative retinopathy. The hemoglobin A_{1c} (HbA_{1c}) value was 7.0 $\pm$ 1.0% (range, 5.6–9.5%) at the time of examination.

Patients were excluded if they had had intraocular surgery during the previous 3 months. Ten patients had previous cataract surgery, and 20 eyes had undergone argon laser panretinal photocoagulation.

As controls (the nondiabetic group), 47 corneas of 28 glaucoma patients (12 men and 16 women), being treated with anti-glaucoma eye drops, were examined at the same hospital during the same period. These controls did not have diabetes mellitus and had not had intraocular surgery during the previous 3 months. Their mean age was 70.0 $\pm$ 7.2 years (range, 43–78 years). There were 17 eyes with POAG and 30 eyes with NTG. The mean number of types of anti-glaucoma eye drops used was 1.6 $\pm$ 0.8 (range, 1–4), and the number used by each patient: one in 27 eyes (57.4%), two in 16 eyes (34.0%), three in 2 eyes (4.3%), and four in 2 eyes (4.3%). Five patients had previous cataract surgery.

The age, sex, number and kinds of anti-glaucoma eye drops, and glaucoma type in the diabetic and nondiabetic groups were not significantly different. All patients gave informed consent for participation in the study.

The severity of the corneal surface damage, ie, the SPK, was evaluated by staining the cornea with fluorescein. The SPK was graded by determining the area and density of the lesion.[4] The SPK index was calculated as the area grade multiplied by the density grade. The tear film status was assessed by a specular reflection video recording system (DR-1, Kowa, Tokyo).[5] The DR-1 camera was focused on a 2.2 $\times$ 3.0 mm area of the central cornea. The images obtained were printed, and the status of the lipid layer was classified into one of 5 grades based on the specific interference color (Grade 1, grayish color and uniform distribution; Grade 2, grayish color with uneven distribution; Grade 3, two or more colors, uneven distribution; Grade 4, numerous colors; and Grade 5, visible corneal surface).

The Schirmer test was performed without topical anesthesia. Standard strips of filter paper were placed in the lateral canthus away from the cornea. After 5 minutes, the paper was gently removed, and the amount of tear secretion measured. The tear BUT was defined as the time between the last complete blink and the first disturbance of the precorneal tear film.

The chi-square test, Mann–Whitney *U*-test, or *t*-tests were used to compare differences between the diabetic and nondiabetic groups.

Results

Only SPK was present as the type of keratoepitheliopathy in both the diabetic and nondiabetic groups. Severer forms of keratoepitheliopathy, such as corneal ulcer or persistent epithelial defect, were not detected. The overall incidence of SPK was 36.1% in the diabetic group and 27.7% in the nondiabetic group on slit-lamp biomicroscopy (Figure 1). The incidence was not significantly different between the two groups ($P = .56$, chi-square test). The index of corneal surface damage, the SPK, in the diabetic group was: one in 5 eyes (13.9%), two in 3 eyes (8.3%), four in 2 eyes (5.6%), six in 2 eyes (5.6%), and nine in 1 eye (2.7%). The index of corneal surface damage

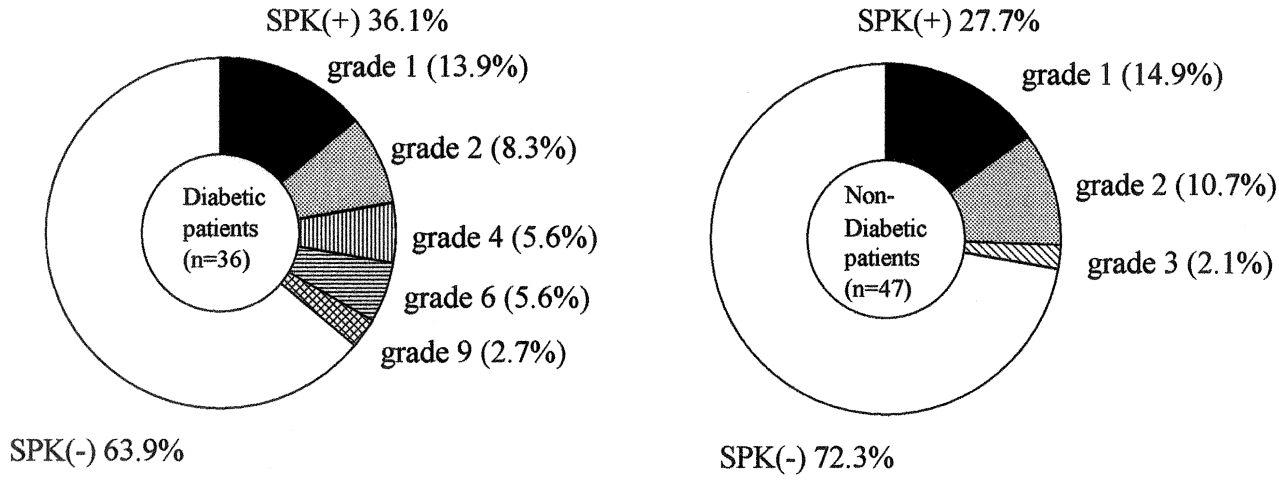

Figure 1. Percentage of superficial punctate keratitis (SPK) in diabetic and nondiabetic patients. (The SPK index: ■: grade 1, ▒: grade 2, ▨: grade 3, ▥: grade 4, ▤: grade 6, ▩: grade 9).

(SPK) in the nondiabetic group was: one in 7 eyes (14.9%), two in 5 eyes (10.7%), and three in 1 eye (2.1%). The mean index of corneal surface damage (SPK) was not significantly different between the diabetic (1.1 ± 2.1) and the nondiabetic (0.4 ± 0.8) groups ($P = .27$, Mann–Whitney test; Figure 2).

The results of the Schirmer test were 11.6 ± 8.4 mm in the diabetic group and 13.2 ± 9.8 mm in the nondiabetic group ($P = .45$, *t*-test). The mean tear BUT was 9.1 ± 3.0 seconds in the diabetic and 9.0 ± 4.1 seconds in the nondiabetic group ($P = .90$, Mann–Whitney test). The mean grade for the tear lipid layer status was 2.1 ± 1.0 in the diabetic and 1.8 ± 0.9 in the nondiabetic group ($P = .19$, *t*-test).

Discussion

We have investigated the influence of diabetes mellitus and/or anti-glaucoma eye drops on keratoepitheliopathy. Earlier, we examined the contribution of ocular and systemic factors on the presence of keratoepitheliopathy in diabetic patients who did not use eye drops.[1] Several glaucoma patients who did not use anti-glaucoma eye drops were included. Keratoepitheliopathy was significantly more frequent in the diabetic patients than in the nondiabetic ones. The uniformity of the tear lipid layer, corneal sensitivity, and tear BUT were significantly worse in the diabetic than in the nondiabetic patients. Diabetes mellitus therefore may induce keratoepitheliopathy and worsen the ocular factors.

We have also examined the contribution of ocular and systemic factors to the anti-glaucoma eye drop-related keratoepitheliopathy in diabetic patients.[3] The occurrence of keratoepitheliopathy was significantly more frequent in diabetic patients who used anti-glaucoma eye drops than in those who did not. The uniformity of the tear lipid layer was significantly worse in the diabetic patients who used anti-glaucoma eye drops than in those who did

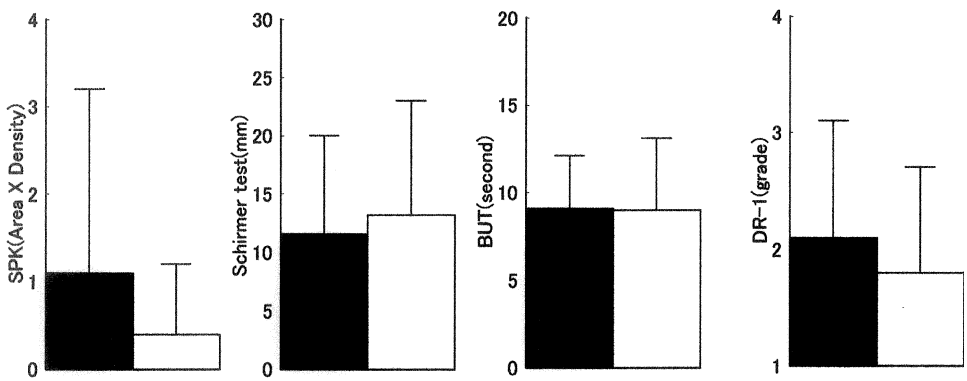

Figure 2. Keratoepitheliopathy and relevant factors. ■: diabetic patients, □: nondiabetic patients.

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not. Anti-glaucoma eye drops therefore may also induce keratoepitheliopathy and worsen the ocular factors (uniformity of the tear lipid layer) even in diabetic patients.

In this study, we evaluated the ocular factors that contributed to the keratoepitheliopathy in glaucoma patients who used anti-glaucoma eye drops and had diabetes mellitus. Keratoepitheliopathy was found more frequently in glaucoma patients who used anti-glaucoma eye drops whether or not they had diabetes mellitus. The SPK index, the Schirmer test values, tear BUT, and uniformity of the tear lipid layer in glaucoma patients with diabetes mellitus who used anti-glaucoma eye drops were similar to those in the glaucoma patients without diabetes mellitus. The reason for these findings is not clear because the corneal surface damage induced by anti-glaucoma eye drops should be severe in both types of cases. Cases with severe SPK indices were seen only in the diabetic group. Therefore, diabetes mellitus may contribute to the severity of SPK in glaucoma patients treated with anti-glaucoma eye drops. In the diabetic group, a multivariate regression analysis was performed to determine how much of the variance in SPK could be explained by systemic (the duration of diabetes mellitus and the value of HbA_{1c}) and retinal (the grade of diabetic retinopathy) factors. The duration of diabetes mellitus ($P = .58$), the value of HbA_{1c} ($P = .57$), and the grade of diabetic retinopathy ($P = .07$) were not significantly correlated with the index of SPK (data not shown).

Concerning keratoepitheliopathy and ocular factors, in glaucoma patients who use anti-glaucoma eye drops, the effects of the diabetes mellitus were not significant, but we must consider the severe cases of keratoepitheliopathy in these patients.

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