The Corneal Endothelium and Thickness in Type II Diabetes Mellitus

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Purpose: To compare the endothelial structure and thickness of the cornea in diabetic and nondiabetic patients, and to evaluate the systemic and ocular factors that contribute to the damage of endothelial cells in diabetic patients.

Methods: The corneal endothelial structure and central corneal thickness (CCT) were investigated in 99 type II diabetic patients (99 eyes) and in 97 nondiabetic patients (97 eyes). The endothelial structure was examined for cell density, coefficient of variation of cell area, and percentage of hexagonal cells. The correlation between CCT and the grade of diabetic retinopathy was evaluated. Multivariate regression analysis was performed to assess systemic factors (patient age, sex, duration of diabetes mellitus, hemoglobin A1c value, glucose in urine, blood urea nitrogen value, and creatine value) and ocular factors (grade of diabetic retinopathy and history of photocoagulation) related to endothelial cell density.

Results: The endothelial cell density was decreased and the coefficient of variation of cell area was increased in diabetic patients ($P < .05$). However, the percentage of hexagonal cells and CCT in diabetic patients was not significantly different from that in nondiabetic patients. CCT was similar regardless of the stage of diabetic retinopathy. Multivariate regression analysis indicated that none of the systemic or ocular factors was significantly correlated with the endothelial cell density.

Conclusions: Corneal endothelial cell structure was damaged, but CCT was not increased in type II diabetic patients. There were no systemic or ocular factors at any one point to induce corneal endothelial damage. Jpn J Ophthalmol 2002;46:65–69 © 2002 Japanese Ophthalmological Society

Key Words: Central corneal thickness, corneal endothelial structure, diabetes mellitus, diabetic retinopathy.

Introduction

Diabetes mellitus is a syndrome characterized by inappropriate hyperglycemia and is chronically associated with microvascular and/or macrovascular complications. Patients with diabetes mellitus often develop not only diabetic retinopathy but also corneal endothelial damage and keratoepitheliopathy such as superficial punctate keratitis, recurrent corneal erosion, and persistent epithelial defects.1–3 Diabetic patients have a high risk of developing persistent stromal edema after pars plana vitrectomy or other intraocular surgical procedures.4 This suggests that diabetic endothelial cells have functional and morphological abnormalities. Functional abnormalities may induce increased corneal autofluorescence as measured by fluorophotometry5,6 as well as increased corneal endothelial permeability,7 although some researchers have reported that corneal endothelial permeability is not increased.5,6,8 Morphological abnormalities may induce a high coefficient of variation of cell area and a decrease in the percentage of hexagonal cells in the corneas of diabetic patients compared with those of nondiabetic patients.2,5,6,9–12 Regarding endothelial cell density in
diabetic patients, one study has reported it to be decreased, while others have reported that it is similar to values in nondiabetic patients. In previous reports, 14–96 corneas of diabetic patients were not enough to evaluate corneal endothelial structure. Functional and morphological abnormalities in diabetic endothelial cells had not yet been defined.

After a decrease in corneal endothelial function, corneal hydration and consequently corneal thickness increase. Increased central corneal thickness (CCT) in patients with type I, type II diabetes, and proliferative retinopathy have been reported in some studies, but others report that CCT is not increased in either type I or type II diabetic patients. Thus, the functional and morphological abnormalities in diabetic endothelial cell and CCT remain to be fully understood.

In diabetic patients, there are many reports using simple regression analysis to evaluate a correlation between endothelial cell density and one of the systemic or ocular factors such as patient age, duration of diabetes, value of hemoglobin A1c (HbA1c), or stage of diabetic retinopathy. There is no report using multiple regression analysis to determine any correlation between diabetic endothelial cell density and the various systemic or ocular factors.

The aim of this study is to compare the endothelial structure and central thickness of a large number of corneas in diabetic and nondiabetic patients, and to evaluate systemic or ocular factors that contribute to the damage of endothelial cells in diabetic patients.

Materials and Methods

Subjects

We studied 99 corneas of 99 type II diabetic patients (53 men and 46 women) at Nadogaya Hospital in November and December 2000 (the diabetic group). Data on the right eye of each patient were used in this study. The mean patient age was 65.5 ± 7.5 years (mean ± standard deviation) (range, 51–78 years). The mean duration of diabetes mellitus was 9.1 ± 8.2 years (range, 6 months–32.8 years). The diabetic patients were classified into three groups: 60 patients without diabetic retinopathy, 33 with nonproliferative retinopathy, 6 with proliferative retinopathy. At the time of examination, the mean value of HbA1c was 6.9 ± 1.3% (range, 4.9–10.2%). The results of tests for glucose in the urine ranged from none to 4+. The mean value of blood urea nitrogen (BUN) was 16.0 ± 5.0 mg/dL (range, 7.5–38.3 mg/dL). The mean value of creatine was 0.9 ± 0.2 mg/dL (range, 0.6–2.1 mg/dL). Sixty-four patients were being treated with topical drugs including pirenosepine (59 patients) and cyanocobalamin (4 patients). Twenty-five eyes had previously undergone argon laser photocoagulation. Patients diagnosed with glaucoma or who had histories of previous intraocular surgery were excluded from this study.

As controls, 97 corneas of 97 patients (52 men and 45 women) were examined at the same place over the same time period (the control group). These controls did not have diabetes mellitus, had not had intraocular surgery, had not undergone argon laser photocoagulation previously, and had no abnormalities of the cornea and conjunctiva. The mean patient age was 67.6 ± 7.3 years (range, 50–79 years). The diagnosis for these patients included cataract (53 eyes), ametropia (28 eyes), asthenopia (8 eyes), and other ocular diseases (8 eyes). Fifty-one patients were being treated with topical drugs including pirenosepine (44 patients) and cyanocobalamin (20 patients). All patients in both groups gave their informed consent for participation in this study.

Methods

The endothelial structure was quantitated by measuring a variety of factors, including cell density, coefficient of variation in cell area, and percentage of hexagonal cells. The central corneal endothelial cells were photographed by specular microscopy, using NONCON ROBO CA (Konan Medical, Kobe). Three central cornea microphotographs were taken and a minimum of 50 cells was counted in each photograph to perform analysis of cell density, coefficient of variation of cell area, and percentage of hexagonal cells. An average of three microphotographs was recorded.

CCT was measured after tonometry with an ultrasonic pachymeter (AL-2000; Tomey, Nagoya) under local anesthesia. The speed of sound (1640 m/s) was used. The pachymeter tip was placed perpendicularly on the cornea and centered over the undilated pupil. An average of five consecutive readings was recorded.

Statistical Analysis

The chi-squared test, the Mann–Whitney U-test, the independent t-test, and the Kruskal–Wallis test were used to compare differences between the diabetic and control groups. We considered values of P < .05 to be statistically significant. Multivariate regression analysis was performed in diabetic patients who could satisfy all systemic and ocular factors (88 eyes).
to determine whether variance in damage to the corneal endothelium could be explained by any of the measured factors. The patient age, sex, duration of diabetes mellitus, HbA$\text{1c}$ value, BUN value, creatine value, glucose value in urine, history of argon laser panretinal photocoagulation, and grade of diabetic retinopathy were used as independent variables. The dependent variable was the cell density of the corneal endothelium.

**Results**

The endothelial cell density was significantly lower in the diabetic group (2493 ± 330 cells/mm$^2$) than in the control group (2599 ± 278 cells/mm$^2$) ($P = .016$, $t$-test) (Figure 1). The coefficient of variation in cell area was significantly higher in the diabetic group (37.2 ± 6.0) than in the control group (35.4 ± 5.0) ($P = .023$, $t$-test). There was no significant difference between the percentages of hexagonal cells in the diabetic group (56.1 ± 8.5%) and the control group (56.7 ± 6.3%) ($P = .51$, Mann–Whitney test).

In addition, there was no significant difference between CCT in the diabetic group (538 ± 36 μm) and the control group (537 ± 38 μm) ($P = .90$, $t$-test) (Figure 1). CCT was 539 ± 36 μm in diabetic patients without retinopathy, 536 ± 33 μm in diabetic patients with nonproliferative retinopathy, and 539 ± 42 μm in diabetic patients with proliferative retinopathy. No significant differences were found between these four groups ($P = .99$, Kruskal–Wallis test) (Figure 2).

Multivariate regression analysis indicated that none of the systemic or ocular factors measured was significantly correlated with the endothelial cell density in the diabetic patients (Table 1).

**Discussion**

There are many reports about corneal endothelial structure in diabetic patients.$^{2,5-14}$ Schultz et al reported that in type II diabetic patients endothelial cell density was similar, coefficient of variation of cell area was increased, and percentage of hexagonal cells was decreased compared with nondiabetic patients.$^2$ Larsson et al reported that the endothelial cell density, coefficient of variation of cell area, and percentage of hexagonal cells all were not significantly different between type II diabetic and nondiabetic patients.$^6$ Roszkowska et al, however, reported in type II diabetic patients a decreased endothelial cell density, an increased coefficient of variation of cell area (polymegathism), and a decreased percentage of hexagonal cells (pleomorphism).$^9$ In Japanese type II diabetic patients, Itoi et al$^{10}$ and Matsuda et al$^{11}$ have reported a similar endothelial cell density, an increased coefficient of variation of cell area, and a decreased percentage of hexagonal cells. In our study, type II diabetic patients showed a decrease in endothelial cell density and a higher coefficient of variation of cell area, but did not show a decrease in percentage of hexagonal cells. The endothelial cell density in diabetic patients decreased at 4.1% compared with nondiabetic patients. Roszkowska et al

![Figure 1. Corneal endothelial morphology and central corneal thickness in diabetic group (■) and control group (□) (endothelial cell density, coefficient of variation, central corneal thickness: $t$-test; percentages of hexagonal cells: Mann–Whitney U-test, $*P < .05$).](image-url)
observed cell density in type II diabetes was decreased at 5% and significantly lower than that in age-matched nondiabetic patients. In our study, the percentage of hexagonal cells in diabetic patients was almost similar to that in nondiabetic patients. The standard deviation of the percentage of hexagonal cells in diabetic patients (8.5%), however, was higher than that in nondiabetic patients (6.3%). None of the previous reports agrees with our study about the damage to the endothelial structure. There seem to be wide individual variations in the endothelial structural damage caused by diabetes mellitus.

We found that CCT in type II diabetic patients (538 ± 36 μm) was the same thickness as in nondiabetic patients in this study, and was similar to that in previous reports. In type II diabetic patients, CCT was reported as 0.53–0.54 and 0.57 mm, which was similar to nondiabetic patients. Roszkowska et al, however, reported CCT (0.57 mm) in type II diabetic patients was significantly increased compared with nondiabetic patients (P < .05). In type I diabetic patients, CCT was reported as 0.51, 0.54, and 0.56 mm, similar to nondiabetic patients. Others reported CCT was 0.58 mm (P = .01) and 0.58 mm (P < .01), and so significantly increased. Both in type I and type II diabetic patients, CCT values have been controversial.

In type I diabetic patients, there were no significant correlations between duration of diabetes mellitus, fasting blood glucose, and CCT. CCT was significantly increased according to the stage of diabetic retinopathy in type I and type II diabetic patients. Busted et al and Olsen et al reported that the mean CCT was 527 ± 28 μm in nondiabetic patients, 544 ± 28 μm in diabetic patients with nonproliferative retinopathy, and 566 ± 27 μm in diabetic patients with proliferative retinopathy; the difference between the groups was significant. Ravalico et al reported that the mean CCT was 552 ± 26 μm in nondiabetic patients, 543 ± 47 μm in diabetic patients without retinopathy, 550 ± 34 μm in diabetic patients with nonproliferative retinopathy, and 569 ± 38 μm in diabetic patients with proliferative retinopathy. CCT in diabetic patients with proliferative retinopathy was significantly thicker than that in nondiabetic patients. In contrast, in this study we found that CCT was similar regardless of the stage of diabetic retinopathy; moreover, there was no difference in CCT between diabetic and nondiabetic patients.

Endothelial cell density has been reported to show a tendency to decrease with increasing age. Schultz et al reported the endothelial cell density in diabetic patients was not related to age. We found that endothelial cell density was not correlated with patient age. We suggest that in our study the damage to endothelial cells induced by diabetes mellitus was so severe as to negate the influence of age.

<table>
<thead>
<tr>
<th>Factors</th>
<th>Regression Coefficient</th>
<th>Standard Regression Coefficient</th>
<th>P Value*</th>
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<tr>
<td>Sex</td>
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<td>Duration of diabetes mellitus</td>
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<td>Photocoagulation</td>
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<td>0.075</td>
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*P values were calculated by Mann–Whitney U-test.
There is a significant correlation reported between age, duration of diabetes mellitus, value of HbA1c, and endothelial cell density, but not between duration of diabetes mellitus, the stage of diabetic retinopathy, and endothelial cell density. In this study, we evaluated correlations between endothelial cell density and systemic or ocular factors not by simple regression analysis but by multiple regression analysis. Multiple regression analysis indicated that none of the measured factors was significantly related to the endothelial cell density. As diabetes mellitus is a chronic disease, it seems reasonable not to have correlations between systemic or ocular factors at the time of examination and endothelial cell density.

The results of this study might support the theory of structural abnormalities of the corneal endothelium in type II diabetic patients. Corneal endothelial cell structure was damaged, but CCT was not increased in type II diabetic patients. There were no systemic or ocular factors at any one point to induce corneal endothelial damage.

References