Clinical peculiarities of bacterial keratitis in type 1 diabetic patients

Key messages:
Diabetes mellitus is a systemic risk factor for bacterial keratitis.

There are clinical peculiarities of bacterial keratitis in patients with type 1 diabetes mellitus at visit 1.

Compared to nondiabetic, diabetic patients with bacterial keratitis show higher degree of inflammatory reaction in the anterior chamber of the eye at visit 1 as well as 28.8% lower mean corneal sensitivity threshold.

Abstract. The purpose was to define the clinical peculiarities of bacterial keratitis in patients with type 1 diabetes mellitus (DM1) at visit 1.

Methods. We retrospectively reviewed the results of 62 DM1 patients (62 eyes) with bacterial keratitis and 43 nondiabetic patients (43 eyes) with bacterial keratitis of the control group who were referred for visit 1 (before administering the treatment). Research methods were as follows: visual acuity, tonometry, slit-lamp biomicroscopy of anterior and posterior eye segments, bacteriological studies, fluorescein dye test, anterior eye OCT and non-contact corneal esthesiometry.

Results. Compared to nondiabetic, DM1 patients with bacterial keratitis showed higher degree of inflammatory reaction in the anterior chamber of the eye at visit 1 (p<0.05) as well as 28.8% lower mean corneal sensitivity threshold (p<0.05). At visit 1, the degree of decreasing of corneal sensitivity in DM1 patients with bacterial keratitis was higher than in control group (p<0.05). Localization of bacterial keratitis, the degree of pericorneal injection, corneal ulcer defect size and depth, corneal infiltration as well as edema of the corneal tissue surrounding the ulcer did not depend on the presence of diabetes mellitus (p>0.05) at visit 1.

Conclusions. There are clinical peculiarities of bacterial keratitis in patients with type 1 diabetes mellitus at visit 1.

Keywords: diabetes mellitus, bacterial keratitis, corneal sensitivity, corneal sensitivity threshold, inflammatory reaction in the anterior chamber of the eye.

Introduction
A lot of authors suggested that diabetes mellitus (DM) is a systemic risk factor for inflammatory diseases of the cornea [1-14], which are characterized by a more severe course and more often lead to blindness [10-14]. Several studies have reported the occurrence of DM in patients with infectious keratitis.

Retrospective, nationwide, matched cohort study in Taiwan included 239 854 patients with DM showed that patients with DM were 1.35 times (95% CI, 1.24 to 1.48) more likely to develop recurrent corneal erosion than the total sample cohort. In total, during for 8-10 years 1236 patients with DM and 884 controls developed recurrent corneal erosion, resulting in an incidence rate of recurrent corneal erosion in patients with DM (5.87/10 000 person-years) higher than that in the controls (4.23/10 000 person-years) [1].

Badawi et al. have reported that the prevalence of DM was 15.1% out of 245 patients with infective keratitis, attended Mansoura Ophthalmic Center, Egypt from Mar. 2013 to Feb. 2015, and suggested that DM was the predominant systemic predisposing factor [2].

Inoue et al. found that the occurrence of DM was 23.8% in 30 cases of corneal ulcer due to Moraxella
infection; they suggested that DM patients are more prone to Moraxella keratitis [3].

A study from China, included 230 diabetic and 168 nondiabetic patients with infectious keratitis showed statistically significant differences in the incidences of bacterial keratitis in the two groups (P<0.05), but no significant statistical difference was found between fungal keratitis and amoebic keratitis (P>0.05) [4]. The durations of hospitalization and recovery period in diabetic patients with keratitis was longer. Authors conclude that DM was a predisposing factor for bacterial keratitis.

The purpose was to define the clinical peculiarities of bacterial keratitis in patients with type 1 diabetes mellitus (DM1) at visit 1.

Methods

We retrospectively reviewed the results of 62 DM1 patients (62 eyes) with bacterial keratitis and 43 nondiabetic patients (43 eyes) with bacterial keratitis of the control group who were referred for visit 1 (before administering the treatment) to the Kharkiv regional hospital over a period of 10 years between February 2011 and November 2020. Bacterial keratitis was diagnosed on the basis of typical clinical picture and bacteriologically confirmed. The exclusion criteria were as follows: glaucoma, moderate and severe refractive errors, previous eye surgeries.

The study protocol complied with the Declaration of Helsinki and was approved by the Ethics and Bioethics Committee of Kharkiv National Medical University.

There were 27 (43.5%) women and 35 (56.5%) men among DM1 patients with bacterial keratitis. DM1 patient age varied from 18 to 49 years (mean, 30.9±8.4 years). Of the 62 DM1 patients, 8 (12.9%) had a diabetes duration less than 5 years, 28 (45.2%) had a diabetes duration of 5 to 10 years, and 26 (41.9%) had a diabetes duration less than 5 years, 28 (45.2%) had a diabetes duration of more than 10 years. In addition, of the 62 DM1 patients, 12 (19.4%) had adequately controlled diabetes (defined as hemoglobin A1c (HbA1c) level of <7.1-7.5%), 18 (29%) had inadequately controlled diabetes (defined as HbA1c 7.1-7.5%), and 32 (51.6%) had out-of-control diabetes (defined as HbA1c >7.5%). Diabetic polyneuropathy (DPN) was found in all DM1 patients. Of the 62 DM1 patients, 17 (27.4%) had asymptomatic DPN, 21 (33.9%) had symptomatic DPN and 24 (38.7%) had disabling DPN as per the classification of Dyck (1999) [15, 16].

There were 18 (41.9%) women and 25 (58.1%) men among nondiabetic patients with bacterial keratitis of the control group. Nondiabetic patient age varied from 18 to 50 years (mean, 32.7±8.4 years). So, patients of the DM1 group and controls were comparable with regard to sex and age.

Research methods were as follows: visual acuity, tonometry, slit-lamp biomicroscopy of anterior and posterior eye segments, bacteriological studies, fluorescein dye test, anterior eye OCT (TOPCON 3D OCT-2000) and non-contact corneal esthesiometry.

Non-contact corneal esthesiometry was performed with the use of the device we have developed for this purpose [17]. Corneal sensation was assessed at nine specified examination points (superior, superior nasal, superior temporal, nasal, central, temporal, inferior nasal, inferior temporal, and inferior points), and average corneal sensitivity threshold was determined. The following parameters for the novel non-contact air-injection corneal esthesiometer were used: diameter of air jet output orifice, 0.5 mm; pulse duration, 1 s; distance to the corneal surface, 4 mm; and air jet temperature, 20 °C. The minimum air jet force was used initially. Thereafter, the air jet force was gradually increased until the subject reported a sensation of breeze.

The parameters for assessment of changes in bacterial keratitis were as follows: pericorneal injection (mild; moderate; marked); size of corneal ulcer defect (< 2 mm; 2-5 mm; > 5 mm); OCT-measured depth of the corneal ulcer defect (< 1/3 of the corneal thickness; 1/3-2/3 of the corneal thickness; > 2/3 of the corneal thickness); corneal infiltration (epithelial; stromal; diffuse); edema of the corneal tissue surrounding the ulcer (epithelial; stromal; diffuse); inflammatory reaction in the anterior chamber of the eye (mild, 5-10 cells in the field of view; moderate, 10-50 cells in the field of view, keratic precipitates; marked, > 50 cells in the field of view, hypopyon); and reduction in corneal sensitivity (mild, 80-130 mL/min; moderate, 130-150 mL/min; marked, > 150 mL/min).

Statistics

Mean and standard deviation (SD) values as well as ranges for corneal sensitivity threshold were calculated. The Mann-Whitney rank test was used to compare the scores for pericorneal injection, size and depth of the corneal defect, edema of the corneal tissue surrounding the ulcer, corneal infiltration, inflammatory reaction in the anterior chamber of the eye and reduction in corneal sensitivity for DM1 patients with bacterial keratitis and controls. The level of significance p ≤ 0.05 was assumed. Excel 2010 was used to develop the primary data base, and Stata 12 software (Stata Corp., College Station, TX) was used for statistical analyses.

Results

In DM1 patients with bacterial keratitis 25.8% of eyes (16 eyes) had central localization of the disease, 54.8% of eyes (34 eyes) – paracentral one, in 19.4% of eyes (12 eyes) – peripheral one. Localization of bacterial keratitis in nondiabetic patients of the control group was central in 27.9% of eyes (12 eyes), paracentral – in 60.5% of eyes (26 eyes), peripheral – in 11.6% of eyes (5 eyes), was not statistically changed from the parameters of the DM1 patients (p>0.05).

The degree of pericorneal injection in DM1 patients with bacterial keratitis was found marked, moderate and mild in 48.4% (30 eyes), 37.1% (23 eyes) and 14.5% patients (9 eyes), respectively, versus 46.5% (20 eyes), 37.2% (16 eyes) and 16.3% nondiabetic patients (7 eyes) with bacterial keratitis of the control group, respectively, p>0.05.

Corneal ulcer defect size in DM1 patients with bacterial keratitis was found more than 5 mm, 2-5 mm, less than 2 mm in 27.4% (17 eyes), 35.5% (22 eyes) and 37.1% DM1 patients (23 eyes) with bacterial keratitis,
respectively, versus 30.2% (13 eyes), 30.2% (13 eyes) and 39.6% (17 eyes) nondiabetic patients with bacterial keratitis of the control group, respectively, \( p<0.05 \).

In DM1 patients with bacterial keratitis the corneal ulcer defect depth was as deep as more than 2/3 of the corneal thickness in 8% (5 eyes), and as deep as 1/3-2/3 of the corneal thickness in 33.9% (21 eyes), and as deep as less than 1/3 of the corneal thickness in 58.1% (36 eyes). In nondiabetic patients with bacterial keratitis the corneal ulcer defect depth was as deep as more than 2/3 of the corneal thickness in 7% (3 eyes), and as deep as 1/3-2/3 of the corneal thickness in 27.9% (12 eyes), and as deep as less than 1/3 of the corneal thickness in 65.1% (28 eyes), was not statistically changed from the parameters of the DM1 patients (\( p>0.05 \)).

The depth of corneal infiltration in DM1 patients was found diffuse, stromal and epithelial in 8.1% (5 eyes), 62.9% (39 eyes) and 29% patients (18 eyes), respectively, versus 7% (3 eyes), 60.5% (26 eyes) and 32.5% (14 eyes) nondiabetic patients with bacterial keratitis of the control group, respectively, \( p<0.05 \).

The depth of edema of the corneal tissue surrounding the ulcer in DM1 patients with bacterial keratitis was found diffuse, stromal and epithelial in 21% (13 eyes), 40.3% (25 eyes) and 38.7% patients (24 eyes), respectively, versus 20.9% (9 eyes), 39.5% (17 eyes) and 39.5% (17 eyes) nondiabetic patients with bacterial keratitis of the control group, respectively, \( p<0.05 \).

Compared to controls, DM1 patients with bacterial keratitis showed higher degree of inflammatory reaction in the anterior chamber of the eye, \( p<0.05 \) (tab 1).

### Table 1

**Inflammatory reaction in the anterior chamber of the eye score in patients with bacterial keratitis according to the presence of diabetes mellitus**

<table>
<thead>
<tr>
<th>Group</th>
<th>Number (percentage) of patients with particular scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 points</td>
</tr>
<tr>
<td>DM1 patients, n=62</td>
<td>4 (6.5%)*</td>
</tr>
<tr>
<td>Nondiabetic patients, n=43</td>
<td>7 (16.2%)</td>
</tr>
</tbody>
</table>

Note: *, Statistically significant difference between the groups \( p<0.05 \)

The degree of inflammatory reaction in the anterior chamber of the eye in DM1 patients with bacterial keratitis was found marked, moderate and mild in 17.7%, 27.4% and 48.4% patients, respectively, versus 7%, 25.6% and 51.2% nondiabetic patients with bacterial keratitis of the control group, respectively. In 6.5% and 16.2% of DM1 and nondiabetic patient with bacterial keratitis, respectively, inflammatory reaction in the anterior chamber of the eye was not found.

Compared to controls, DM1 patients with bacterial keratitis showed 28.8% lower mean corneal sensitivity threshold, \( p<0.05 \) (tab 2).

### Table 2

**Scores for corneal sensitivity threshold in patients with bacterial keratitis according to the presence of diabetes mellitus**

<table>
<thead>
<tr>
<th>Group</th>
<th>Number (percentage) of patients with particular scores</th>
<th>( M\pm m )</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 points</td>
<td>1 point</td>
<td>2 points</td>
</tr>
<tr>
<td>DM1 patients, n=62</td>
<td>0</td>
<td>6 (9.7%)*</td>
<td>16 (25.8%)*</td>
</tr>
<tr>
<td>Nondiabetic patients, n=43</td>
<td>0</td>
<td>23 (53.5%)</td>
<td>17 (39.5%)</td>
</tr>
</tbody>
</table>

Note: *, Statistically significant difference between the groups \( p<0.05 \)

Mean corneal sensitivity threshold in DM1 patients with bacterial keratitis was 164.8±29.4 ml/min, ranged from 119.8 to 235.6 ml/min. Mean corneal sensitivity threshold in nondiabetic patients with bacterial keratitis of the control group was 128±20.2 ml/min, ranged from 97.5 to 194.3 ml/min. The degree of decreasing of corneal sensitivity in DM1 patients with bacterial keratitis was higher than in nondiabetic patients of the control group, \( p<0.05 \). Severely, moderately and mildly decreased corneal sensitivity was found in 64.5%, 25.8% and 9.7% patients, respectively, in DM1 patients with bacterial keratitis, versus 7%, 39.5% and 53.5% nondiabetic patients with bacterial keratitis of the control group, respectively.

**Discussion**

DM is a systemic risk factor for inflammatory diseases of the cornea [1-14], especially for bacterial keratitis [3, 4]. However, there is few information about the clinical peculiarities of bacterial keratitis in DM1 patients.

We defined that localization of bacterial keratitis, the degree of pericorneal injection, corneal ulcer defect size and depth, corneal infiltration as well as edema of the corneal tissue surrounding the ulcer did not depend on the presence of diabetes mellitus (\( p>0.05 \)) at visit 1. But compared to nondiabetic patients with bacterial keratitis, DM1 patients with bacterial keratitis showed higher degree of inflammatory reaction in the anterior chamber of the eye at visit 1, \( p<0.05 \). Our data agree with the fact that DM patients have abnormal inflammatory reaction [18-20]. It was suggested that the janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway to be activated in the setting of diabetes. This pathway is normally
activated by interferons, interleukins and growth factors. Recio and colleagues demonstrated that systemic administration of a cell permeable suppressor of cytokine signaling-1 (SOCS1) peptide, containing the kinase inhibitory region, reduced measures of inflammation in diabetic apolipoprotein E (ApoE)-deficient mice [19]. In another study, Gray et al. found that deficiency in the hydrogen peroxide-generating NADPH oxidase isoform 4 (NOX4) resulted in augmented pro-inflammatory status, measured as circulating levels of CCL2 and vascular gene expression of several cytokines in ApoE-deficient diabetic mice [20].

Our present study revealed that compared to controls, DM1 patients with bacterial keratitis showed 28.8% lower mean corneal sensitivity threshold, **p**<0.05. The degree of decreasing of corneal sensitivity in DM1 patients with bacterial keratitis was higher than in nondiabetic patients of the control group (**p**<0.05). These may be due to diabetic corneal neuropathy - pathological changes of corneal innervations in diabetic patients. Diabetic corneal neuropathy is a part and an important early indicator of diabetic neuropathy [21]. Chronic hyperglycaemia leads to a variety of metabolic changes, such as the accumulation of advanced glycation end products, increased polyol pathway flux, reactive oxygen species production, as well as activation of protein kinase C pathway, causing corneal degeneration and hyperplasia of neural cells [14, 22]. Decreased corneal sensitivity in diabetic patients is a sign of corneal diabetic neuropathy [14, 21, 22]. There were a lot of studies which showed decreased corneal sensitivity in DM patients [23-29] and abnormalities of corneal nerve structure [24, 28, 30-33]. But still that there was no information in the literature concerning the corneal sensitivity in DM patients with bacterial keratitis.

Corneal diabetic neuropathy may influence on the duration and prognosis of bacterial keratitis in DM1 patients, so future studies should be done in order to define that.

Management of bacterial keratitis in DM1 patients should take into account diabetic corneal neuropathy as well.

This study has some limitations because of small sample size. To our mind, quantitative evaluation of the morphology of corneal nerves due to recent advancements in corneal nerve imaging and software allow to define the possible associated pathogenic mechanisms for corneal ulcer in DM patients better.

**Conclusions**

There are clinical peculiarities of bacterial keratitis in patients with type 1 diabetes mellitus at visit 1. Compared to nondiabetic, diabetic patients with bacterial keratitis show higher degree of inflammatory reaction in the anterior chamber of the eye, as well as 28.8% lower mean corneal sensitivity threshold.

**Ethical approval:** “All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.”

**Informed consent:** “Informed consent was obtained from all individual participants included in the study.”

**Conflict of Interest:** The authors declare that they have no conflict of interest.

**Financial disclosures:** The authors have no financial interest in any of the materials used in this study.

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