International Journal of Ophthalmology & Visual Science
2021; 6(2): 115-121
http://www.sciencepublishinggroup.com/j/ijovs
doi: 10.11648/j.ijovs.20210602.19
ISSN: 2637-384X (Print); ISSN: 2637-3858 (Online)

Bacterial Keratitis in Type 1 Diabetic Patients: Course and Consequences

Olesia Zavoloka, Pavlo Bezditko

Department of Ophthalmology, Kharkiv National Medical University, Kharkiv, Ukraine

Email address:
olesya_zavoloka@yahoo.com (O. Zavoloka)

To cite this article:
Olesia Zavoloka, Pavlo Bezditko. Bacterial Keratitis in Type 1 Diabetic Patients: Course and Consequences. *International Journal of Ophthalmology & Visual Science.* Vol. 6, No. 2, 2021, pp. 115-121. doi: 10.11648/j.ijovs.20210602.19

Received: May 26, 2021; **Accepted**: June 8, 2021; **Published**: June 15, 2021

Abstract: *The purpose* was to define the peculiarities of the course and consequences of bacterial keratitis in patients with type 1 diabetes mellitus (DM1) depending on the stage of its severity. *Methods.* 34 DM1 patients (34 eyes) with bacterial keratitis whose initial bacteriological examination revealed pathogen sensitivity to the antibiotic ofloxacin participated in this study. All patients were treated topically with ofloxacin, antiseptics, repairing agents, antioxidants, mydriatics, artificial tears and systemically with anti-inflammatory agents. Patients were divided into two groups according to the severity of bacterial keratitis at the first visit. Research methods were as follows: visual acuity, tonometry, slit-lamp biomicroscopy of anterior and posterior eye segments, fluorescein dye test, non-contact corneal esthesiometry, anterior eye OCT and bacteriological studies. *Results.* Compared to the stage I, DM1 patients with stage II severity bacterial keratitis showed higher degree of pericorneal injection, larger and deeper corneal ulcer defect, deeper corneal infiltration and edema, higher mean corneal sensitivity threshold at all time point of the study, $p<0.05$. DM1 patients with stage II severity bacterial keratitis were more prone for longer duration of the disease and worse consequences. Therefore, on day 24 in 33.3% diabetic patients with stage II severity bacterial keratitis corneal ulcer was not found to be healed. *Conclusions.* Course and consequences of bacterial keratitis in type 1 diabetes mellitus patients depend on the stage of severity of bacterial keratitis.

Keywords: Diabetes Mellitus, Bacterial Keratitis, Course of Bacterial Keratitis Course, Consequences of Bacterial Keratitis

1. Introduction

Despite recent advances in the management of diabetes mellitus (DM) and infectious diseases, DM patients remain at increased risk of infection. A lot of factors, including abnormal inflammatory reaction and attenuated immune responsiveness as well as diabetic tissue damage, may play a key role in peculiarities of healing process in DM patients and cause chronical wounds [1-5].

It is known that DM is a systemic risk factor for keratitis [6-19]. There were several studies which reported the high occurrence of DM in patients with keratitis.

Chang et al. reported that DM patients are 1.35 times more likely to develop recurrent corneal erosion than the total sample cohort. The study was done in Taiwan, lasted for 10 years and included 239 854 DM patients. It was retrospective, nationwide, matched cohort study. An incidence rate of recurrent corneal erosion in DM patients (5.87/10 000 person-years) was higher than that in the controls (4.23/10 000 person-years) [6].

Badawi et al. suggested that DM is the predominant systemic predisposing factor for infective keratitis. They conducted a study in Mansoura Ophthalmic Center, Egypt which lasted from Mar. 2013 to Feb. 2015. The study has shown that the prevalence of DM is 15.1% out of 245 patients with infective keratitis [7].

Inoue et al. reported that DM patients are more prone to Moraxella keratitis. They found that 23.8% patients from 30 cases of corneal ulcer due to Moraxella infection had DM [8].

Wang et al. found the high incidences of bacterial keratitis in DM patients and long recovery period in that group. The study was conducted in Chine and included 230 diabetic and 168 nondiabetic patients with infectious keratopathy [9].

But there is few information about the course and consequences of bacterial keratitis in DM patients.

The purpose was to define the peculiarities of the course and consequences of bacterial keratitis in patients with type 1 diabetes mellitus (DM1) depending on the stage of its severity.

2. Methods

34 DM1 patients (34 eyes) with bacterial keratitis who were referred the Kharkiv Regional Clinical Hospital and whose initial bacteriological examination (taken before treatment) revealed pathogen sensitivity to the antibiotic ofloxacin participated in this study. Bacterial keratitis was bacteriologically confirmed. The exclusion criteria were as follows*:* glaucoma, previous eye surgeries, moderate and severe refractive errors,.

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Kharkiv National Medical University (5.12.2018/№ 11). Informed consent was obtained from all individual participants included in the study. The participant has consented to the submission of the case report to the journal.

All patients were treated topically with ofloxacin (until corneal smears and scrapings were bacteriologically negative), antiseptics, repairing agents, antioxidants, mydriatics, artificial tears (0.15-0.4% hyaluronic acid) and systemically with anti-inflammatory agents.

Patients were divided into two groups according to the severity of bacterial keratitis at the first visit. We developed a scheme for determination of the severity of bacterial keratitis which includes 8 signs. Depending on the severity, each of sign was evaluated in points (0, 1, 2, 3) with the following calculation of the sum of points: localization of keratitis (1: peripheral; 2: paracentral; 3: central), inflammatory reaction in the anterior chamber of the eye (1: mild, 5-10 cells in the field of view; 2: moderate, 10-50 cells in the field of view, flair, precipitates; 3: marked,> 50 cells in the field of view, fibrin deposits, hypopion), pericorneal injection (1: mild; 2: moderate; 3: marked); corneal ulcer defect size (1: < 2 mm; 2: 2-5 mm; 3: >5 mm); OCT-measured corneal ulcer defect depth (1: < 1/3 of the corneal thickness; 2: 1/3-2/3 of the corneal thickness; 3: >2/3 of the corneal thickness); edema of the corneal tissue surrounding the ulcer (1: epithelial; 2: stromal; 3: diffuse); corneal infiltration (1: epithelial; 2: stromal; 3: diffuse); and reduction in corneal sensitivity (1: mild, 80-130 mL/min; 2: moderate, 130-150 mL/min; 3: marked, >150 mL/min). The maximum sum of points, according to our scheme, was 24. Stage I severity bacterial keratitis was determined with a total score of ≤ 14 points, stage II - 15-21 points, stage III - ≥ 22 points or in case of loss of the eye threatening conditions (descemetocele, corneal perforation, endophthalmitis, panophthalmitis).

The first group was formed by 15 DM1 patients with stage I severity bacterial keratitis, the second group - by 19 DM1 patients with stage II severity bacterial keratitis. Patients with stage III severity bacterial keratitis required therapeutic keratoplasty. The Kharkiv Regional Clinical Hospital is not specialized in keratoplasty so we did not include DM1 patients with stage III severity bacterial keratitis in our study.

In the first group, patient age varied from 18 to 48 years (mean, 27.8±8.0 years), male:female ratio was 8:7. Diabetic polyneuropathy (DPN) was diagnosed in all patients of the first group: 6 (40%) of the 15 patients had asymptomatic DPN, 3 (20%) had symptomatic DPN, and 6 (40%) had disabling DPN [20, 21]. Moreover, 4 (26.7%) of the 15 patients of the first group had adequately controlled DM1 (hemoglobin A1c (HbA1c) level of <7.1%), 4 (26.7%) had inadequately controlled DM1 (HbA1c level of 7.1-7.5%), and 7 (46.6%) had out-of-control DM1 (HbA1c ≥7.5%). In addition, 2 (13.3%) of the 15 patients of the first group had a DM1 duration of less than 5 years, 7 (46.7%) - of 5 to 10 years, and 6 (40%) - of more than 10 years.

In the second group, patient age varied from 18 to 48 years (mean, 32.1±8.9 years), male:female ratio was 10:9. DPN was diagnosed in all patients of the second group: 10 (52.6%) of the 19 patients had symptomatic DPN, and 9 (47.4%) had disabling DPN. Moreover, 6 (31.6%) of the 19 patients of the second group had inadequately controlled DM1, and 13 (68.4%) had out-of-control DM1. In addition, 8 (42.1%) of the 19 patients of the second group had a DM1 duration of 5 to 10 years, and 11 (57.9%) - of more than 10 years.

All examinations were made on day 1 (before administering the treatment), day 3, day 7, day 10, day 14, day 17, day 21 and day 24. After 14 days, some patients (10 patients) from the second group changed the treatment that is why their results were not taking into account for day 17, day 21, day 24.

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

Non-contact corneal esthesiometry was performed with the help of the device we have made for this purpose [22]. Corneal sensation was assessed at nine specified examination points (superior, superior temporal, superior nasal, central, temporal, nasal, inferior temporal, inferior nasal, and inferior points), and average corneal sensitivity threshold was calculated. We used the following parameters for the novel non-contact air-jet corneal esthesiometer: diameter of air jet output orifice, 0.5 mm; distance to the corneal surface, 4 mm; pulse duration, 1 s; and air jet temperature, 20 °C. Initially was used the minimum air jet force. Then, the air jet force was gradually increased until the patient felt a sensation of breeze.

Statistics

We used Excel 2010 to develop the primary data base, and Stata 12 software (Stata Corp., College Station, TX) for statistical analyses. To compare the scores for localization of keratitis, inflammatory reaction in the anterior chamber of the eye, pericorneal injection, corneal ulcer defect size and depth, edema of the corneal tissue surrounding the ulcer, corneal infiltration, and reduction in corneal sensitivity for the first and second groups the Mann-Whitney rank test was used. For corneal sensitivity threshold mean, standard deviation (SD) values, and ranges were calculated. $p \leq 0.05$ was considered statistically significant.

3. Results

Repeated bacteriological examination (taken 1 week after

initiation of treatment) of corneal scrapings and smears confirmed the absence of microorganisms in all participants of the study.

In the first group, 20% of eyes (3 eyes) had central localization of the bacterial keratitis, 53.3% of eyes (8 eyes) – paracentral one, in 26.7% of eyes (4 eyes) – peripheral one. Localization of bacterial keratitis of the second group was central in 26.3% of eyes (5 eyes), paracentral – in 63.2% of eyes (12 eyes), peripheral – in 10.5% of eyes (2 eyes), was not statistically changed from the parameters of the first group ($p>0.05$).

At the first visit, patients of the second group showed higher degree of inflammatory reaction in the anterior chamber of the eye in comparison with the first group, $p<0.05$ (table 1). The degree of inflammatory reaction in the anterior chamber of the eye in the first group was found marked, moderate and mild in 0%, 20% and 73.3% patients, respectively, versus 31.6%, 47.4% and 21% patients of the second group, respectively. In 6.7% patient of the first group inflammatory reaction in the anterior chamber of the eye was not found.

Table 1. *Inflammatory reaction in the anterior chamber of the eye score in diabetic patients according to the degree of severity of bacterial keratitis at the first visit.*

Group	Number (percentage) of patients with particular scores			
	0 points	1 point	2 points	3 points
First, n=15	1 (6.7%)*	11 (73.3%)	3 (20%)	0
Second, n=19	0	4 (21%)	9 (47.4%)	6 (31.6%)

Note: *, significant difference between the groups $p<0.05$

Compared to the first group, patients of the second group showed higher degree of pericorneal injection at all time point of the study, $p<0.05$ (table 2). Conjunctival color appeared to normalize in all patients of the first group on day 21, while mild pericorneal injection was still present in 33.3% of the second group on day 24.

Table 2. *Pericorneal injection scores in diabetic patients according to the degree of severity of bacterial keratitis at different time point of the study.*

Day/score	Group	Number (percentage) of patients with particular scores			
		0 points	1 point	2 points	3 points
1st day	First, n=15	0	4 (26,7%)*	6 (40%)	5 (33,3%)*
	Second, n=19	0	0	8 (42,1%)	11 (57,9%)
3rd day	First, n=15	1 (6,7%)	4 (26,7%)*	7 (46,7%)	3 (20%)*
	Second, n=19	0	1 (5,3%)	11 (57,9%)	7 (36,8%)
7th day	First, n=15	1 (6,7%)	10 (66,7%)*	4 (26,7%)*	0
	Second, n=19	0	9 (47,4%)	10 (52,6%)	0
10th day	First, n=15	5 (33,3%)*	9 (60%)	1 (6,7%)*	0
	Second, n=19	0	12 (63,2%)	7 (36,8%)	0
14th day	First, n=15	9 (60%)*	6 (40%)*	0*	0
	Second, n=19	0	15 (78,9%)	4 (21,1%)	0
17th day	First, n=15	12 (80%)*	3 (20%)*	0	0
	Second, n=9	2 (22,2%)	6 (66,7%)	1 (11,1%)	0
21st day	First, n=15	15 (100%)*	0*	0	0
	Second, n=9	3 (33,3%)	6 (66,7%)	0	0
24th day	First, n=15	15 (100%)*	0*	0	0
	Second, n=9	6 (66,7%)	3 (33,3%)	0	0

Note: *, significant difference between the groups for a particular time point $p<0.05$

At all time point of the study, patients of the second group showed larger and deeper corneal ulcer defect in comparison with the first group, $p<0.05$ (table 3, table 4). In all patients of the first group, the corneal wound was fully epithelialized on day 17. While in 33.3% patients of the second group an ulcer defect was still present on day 24; the defect size was less 2 mm and as deep as less than 1/3 of the corneal thickness in 11.1% patients, the defect size was less 2-5 mm and as deep as 1/3-2/3 of the corneal thickness in 22.2% patients).

Table 3. *Scores for corneal ulcer defect size in diabetic patients according to the degree of severity of bacterial keratitis at different time point of the study.*

Day/score	Group	Number (percentage) of patients with particular scores			
		0 points	1 point	2 points	3 points
1st day	First, n=15	0	10 (66,7%)*	5 (33,3%)	0*
	Second, n=19	0	0	8 (42,1%)	11 (57,9%)
3rd day	First, n=15	0	10 (66,7%)*	5 (33,3%)	0*
	Second, n=19	0	0	9 (47,3%)	10 (52,6%)
7th day	First, n=15	2 (13,3%)*	10 (66,7%)*	3 (20%)*	0*
	Second, n=19	0	0	11 (57,9%)	8 (42,1%)

Day/score	Group	Number (percentage) of patients with particular scores			
		0 points	1 point	2 points	3 points
10th day	First, n=15	8 (53,3%)*	6 (40%)*	1 (6,7%)*	0*
	Second, n=19	0	1 (5,3%)	11 (57,9%)	7 (36,8%)
14th day	First, n=15	14 (93,3%)*	1 (6,7%)	0*	0*
	Second, n=19	0	3 (15,8%)	10 (52,6%)	6 (31,6%)
17th day	First, n=15	15 (100%)*	0*	0*	0
	Second, n=9	0	2 (22,2%)	6 (66,7%)	1 (11,1%)
21st day	First, n=15	15 (100%)*	0*	0*	0
	Second, n=9	2 (22,2%)	3 (33,3%)	4 (44,4%)	0
24th day	First, n=15	15 (100%)*	0	0*	0
	Second, n=9	6 (66,7%)	1 (11,1%)	2 (22,2%)	0

Note: *, significant difference between the groups for a particular time point $p<0.05$

Table 4. *Scores for corneal ulcer defect depth in diabetic patients according to the degree of severity of bacterial keratitis at different time point of the study.*

Day/score	Group	Number (percentage) of patients with particular scores		
		0 points	1 point	2 points
1st day	First, n=15	0	11 (73,3%)*	4 (26,7%)*
	Second, n=19	0	9 (47,4%)	10 (52,6%)
3rd day	First, n=15	0	11 (73,3%)*	4 (26,7%)*
	Second, n=19	0	9 (47,4%)	10 (52,6%)
7th day	First, n=15	2 (13,3%)*	9 (60%)*	4 (26,7%)*
	Second, n=19	0	9 (47,4%)	10 (52,6%)
10th day	First, n=15	8 (53,3%)*	6 (40%)	1 (6,7%)*
	Second, n=19	0	10 (52,6%)	9 (47,4%)
14th day	First, n=15	14 (93,3%)*	1 (6,7%)*	0*
	Second, n=19	0	11 (57,9%)	8 (42,1%)
17th day	First, n=15	15 (100%)*	0*	0*
	Second, n=9	0	6 (66,7%)	3 (33,3%)
21st day	First, n=15	15 (100%)*	0*	0*
	Second, n=9	2 (22,2%)	4 (44,4%)	3 (33,3%)
24th day	First, n=15	15 (100%)*	0	0*
	Second, n=9	6 (66,7%)	1 (11,1%)	2 (22,2%)

Note: *, significant difference between the groups for a particular time point $p<0.05$

Compared to the first group, patients of the second group showed deeper corneal infiltration at all time point of the study, $p<0.05$ (table 5). Corneal infiltration was resolved in all patients of the first group on day 14, and in the second group, on day 21.

Table 5. *Scores for corneal infiltration in diabetic patients according to the degree of severity of bacterial keratitis at different time point of the study.*

Day/score	Group	Number (percentage) of patients with particular scores		
		0 points	1 point	2 points
1st day	First, n=15	0	8 (53,3%)*	7 (46,7%)*
	Second, n=19	0	0	19 (100%)
3rd day	First, n=15	1 (6,7%)	12 (80%)*	2 (13,3%)*
	Second, n=19	0	5 (26,3%)	14 (73,7%)
7th day	First, n=15	8 (53,3%)*	7 (46,7%)*	0*
	Second, n=19	0	13 (68,4%)	6 (31,6%)
10th day	First, n=15	13 (86,7%)*	2 (13,3%)*	0*
	Second, n=19	2 (10,5%)	13 (68,4%)	4 (21,1%)
14th day	First, n=15	15 (100%)	0	0
	Second, n=19	10 (52,6%)*	9 (47,4%)*	0
17th day	First, n=15	15 (100%)	0	0
	Second, n=9	7 (77,8%)*	2 (22,2%)*	0
21st day	First, n=15	15 (100%)	0	0
	Second, n=9	9 (100%)	0	0

Note: *, significant difference between the groups for a particular time point $p<0.05$

At all time point of the study patients of the second group showed deeper edema of the corneal tissue surrounding the ulcer in comparison with the first group, $p<0.05$ (table 6). Edema of the corneal tissue surrounding the ulcer was completely resolved in all patients of the first group on day 21, and in the second group, on day 24.

Table 6. *Scores for edema of the corneal tissue surrounding the ulcer in diabetic patients according to the degree of severity of bacterial keratitis at different time point of the study.*

Day/score	Group	Number (percentage) of patients with particular scores			
		0 points	1 point	2 points	3 points
1st day	First, n=15	0	7 (46,7%)*	8 (53,3%)*	0*
	Second, n=19	0	6 (31,6%)	5 (26,3%)	8 (42,1%)
3rd day	First, n=15	1 (6,7%)	6 (40%)	8 (53,3%)*	0*
	Second, n=19	0	6 (31,6%)	6 (31,6%)	7 (36,8%)
7th day	First, n=15	2 (13,3%)*	9 (60%)*	4 (26,7%)*	0
	Second, n=19	10 (52,6%)	7 (36,8%)	2 (10,5%)	0
10th day	First, n=15	8 (53,3%)	6 (40%)	1 (6,7%)	0
	Second, n=19	10 (52,6%)	8 (42,1%)	1 (5,3%)	0
14th day	First, n=15	13 (86,7%)*	2 (13,3%)*	0	0
	Second, n=19	13 (68,4%)	6 (31,6%)	0	0
17th day	First, n=15	14 (93,3%)*	1 (6,7%)*	0	0
	Second, n=9	7 (77,8%)	2 (22,2%)	0	0
21st day	First, n=15	15 (100%)	0	0	0
	Second, n=9	8 (88,9%)	1 (11,1%)	0	0
24th day	First, n=15	15 (100%)	0	0	0
	Second, n=9	9 (100%)	0	0	0

Note: *, significant difference between the groups for a particular time point $p<0.05$

Compared to the first group, patients of the second group showed higher mean corneal sensitivity threshold at all time point of the study, $p<0.05$ (table 7). At visit 1, severely, moderately and mildly decreased corneal sensitivity was found in 33.3%, 46.7% and 20% patients of the first group, respectively, while severely decreased corneal sensitivity was noted in all patients of the second group. On day 24 of the study, all patients of the first group showed mildly decreased corneal sensitivity, while 22.2% and 77.8% of the second group, moderately and mildly decreased corneal sensitivity, respectively.

Table 7. *Scores for corneal sensitivity threshold in diabetic patients according to the degree of severity of bacterial keratitis at different time point of the study.*

Day/score	Group	Number (percentage) of patients with particular scores			
		0 points	1 point	2 points	3 points
1st day	First, n=15	0	3 (20%)*	7 (46,7%)*	5 (33,3%)*
	Second, n=19	0	0	0	19 (100%)
3rd day	First, n=15	0	9 (60%)*	3 (20%)*	3 (20%)*
	Second, n=19	0	0	1 (5,3%)	18 (94,7%)
7th day	First, n=15	0	9 (60%)*	5 (33,3%)*	1 (6,7%)*
	Second, n=19	0	0	2 (10,5%)	17 (89,5%)
10th day	First, n=15	0	9 (60%)*	6 (40%)*	0*
	Second, n=19	0	2 (10,5%)	3 (15,8%)	14 (73,7%)
14th day	First, n=15	0	14 (93,3%)*	1 (6,7%)*	0*
	Second, n=19	0	2 (10,5%)	8 (42,1%)	9 (47,4%)
17th day	First, n=15	0	15 (100%)*	0*	0*
	Second, n=9	0	2 (22,2%)	5 (55,6%)	2 (22,2%)
21st day	First, n=15	0	15 (100%)*	0*	0*
	Second, n=9	0	3 (33,3%)	4 (44,4%)	2 (22,2%)
24th day	First, n=15	0	15 (100%)*	0*	0
	Second, n=9	0	7 (77,8%)	2 (22,2%)	0

Note: *, significant difference between the groups for a particular time point $p<0.05$

The consequences of bacterial keratitis in the second group were found to be worse in comparison to the first group, $p<0.05$. Bacterial corneal ulcer resulted in nubecula corneae and macula corneae in 3 (20%) and 4 (26.7%), respectively, patients of the first group. While in the second group, on day 24 corneal ulcer was not found to be healed in 3 (33.3%) patients; 1 (11.1%) showed central corneal defects sized less than 2 mm and as deep as less than 1/3 of the corneal thickness, and 2 (22.2%) showed paracentral corneal defects sized 2-5 mm and as 1/3-2/3 of the corneal thickness, and these defects were accompanied by mild pericorneal injection. This was the reason why three patients of the second group were recommended to have surgery, specifically, therapeutic keratoplasty. Bacterial corneal ulcer resulted in nubecula corneae and macula corneae in 4 (44.4%) and 2 (22.2%), respectively, patients of the second group.

4. Discussion

DM increases the risk of keratitis [6-19], especially bacterial one [8, 9]. However, there is few information about the peculiarities of the course and consequences of bacterial

keratitis in DM patients depending on the stage its severity.

Our present study revealed that compared to the stage I severity bacterial keratitis, diabetic patients with stage II severity bacterial keratitis are more prone to longer duration of the disease and worse consequences. Therefore, on day 24 in 3 (33.3%) diabetic patients with stage II severity bacterial keratitis corneal ulcer was not found to be healed, and that was the reason why they were recommended to have surgery, specifically, therapeutic keratoplasty.

Our data agree with the fact that DM patients have abnormal wound healing and are more prone to chronic inflammation [1-5]. 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 [4]. 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 [5].

Our present study revealed that compared to the stage I severity bacterial keratitis, diabetic patients with stage II severity bacterial keratitis showed higher mean corneal sensitivity threshold at all time point of the study, $p<0.05$. These may be due to diabetic corneal neuropathy which is a part of diabetic neuropathy [23] and may influence on the duration and prognosis of bacterial keratitis in DM1 patients. 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 neuronal degeneration and apoptosis of neural cells [19, 24]. Decreased corneal sensitivity in diabetic patients is a sign of corneal diabetic neuropathy [19, 23, 24]. There were made a lot of studies which showed decreased corneal sensitivity in DM patients [25-31] and abnormalities of corneal nerve structure [26, 30, 32-35]. But still that there was no information in the literature concerning the corneal sensitivity in DM patients with bacterial keratitis.

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.

5. Conclusions

Course and consequences of bacterial keratitis in type 1 diabetes mellitus patients depend on the stage of severity of bacterial keratitis. Compared to stage I severity bacterial keratitis, diabetic patients with stage II severity bacterial keratitis are more prone to longer duration of the disease and worse consequences. Diabetic patients with stage II severity bacterial keratitis showed higher mean corneal sensitivity threshold at all time point of the study than those with stage I severity bacterial keratitis.

Conflict of Interest

The authors declared that they have no conflict of interest.

References

[1] Peleg AY, Weerarathna T, McCarthy JS, Davis TM (2007) Common infections in diabetes: pathogenesis, management and relationship to glycaemic control. Diabetes Metable Res Rev 23 (1): 3-13. https://doi.org/10.1002/dmrr.682

[2] Shah BR, Hux JE (2003) Quantifying the risk of infectious diseases for people with diabetes. Diabetes Care 26: 510–513.

[3] Kanter JE, Bornfeldt KE (2016) Impact of Diabetes Mellitus. Arterioscler Thromb Vasc Biol 36 (6): 1049-1053. https://doi:10.1161/ATVBAHA.116.307302

[4] Recio C, Oguiza A, Lazaro I, Mallavia B, Egido J, Gomez-Guerrero C (2014) Suppressor of cytokine signaling 1-derived peptide inhibits Janus kinase/signal transducers and activators of transcription pathway and improves inflammation and atherosclerosis in diabetic mice. Arterioscler Thromb Vasc Biol 34 (9): 1953-6190. https://doi:10.1161/ATVBAHA.114.304144.

[5] Gray SP, Di Marco E, Kennedy K, Chew P, Okabe J, El-Osta A, Calkin AC, Biessen EA, Touyz RM, Cooper ME, Schmidt HH, Jandeleit-Dahm KA (2015) Reactive Oxygen Species Can Provide Atheroprotection via NOX4-Dependent Inhibition of Inflammation and Vascular Remodeling. Arterioscler Thromb Vasc Biol 36 (2): 295-307. https://doi:10.1161/ATVBAHA.115.307012.

[6] Chang YS, Tai MC, Ho CH, Chu CC, Wang JJ, Tseng SH, Jan RL (2020) Risk of Corneal Ulcer in Patients with Diabetes Mellitus: A Retrospective Large-Scale Cohort Study. Sci Rep 30; 10 (1): 7388. https://doi.org/10.1038/s41598-020-64489-0.

[7] Badawi AE, Moemen D, El-Tantawy NL (2017) Epidemiological, clinical and laboratory findings of infectious keratitis at Mansoura Ophthalmic Center, Egypt. Int J Ophthalmol 18; 10 (1): 61-67. https://doi.org/10.18240/ijo.2017.01.10

[8] Inoue H, Suzuki T, Inoue T, Hattori T, Nejima R, Todokoro D, Hoshi S, Eguchi H, Miyamoto H, Ohashi Y (2015). Clinical Characteristics and Bacteriological Profile of Moraxella Keratitis. Cornea 34 (9): 1105-1109. https://doi.org/10.1097/ICO.0000000000000470

[9] Wang B, Yang S, Zhai HL, Zhang YY, Cui CX, Wang JY, Xie LX (2018) A comparative study of risk factors for corneal infection in diabetic and non-diabetic patients. Int J Ophthalmol 18; 11 (1): 43-47. https://doi.org/10.18240/ijo.2018.01.08

[10] Almizel A, Alsuhaibani FA, Alkaff AM, Alsaleh AS, Al-Mansouri SM (2019) Bacterial Profile and Antibiotic Susceptibility Pattern of Bacterial Keratitis at a Tertiary Hospital in Riyadh. Clin Ophthalmol 20; 13: 2547-2552. https://doi.org/10.2147/OPTH.S223606

[11] Vieira-Potter VJ, Karamichos D, Lee DJ (2016) Ocular Complications of Diabetes and Therapeutic Approaches. Biomed Res Int 2016: 3801570. https://doi.org/10.1155/2016/3801570

[12] Ormerod LD, Hertzmark E, Gomez DS, Stabiner RG, Schanzlin DJ, Smith RE (1987) Epidemiology of microbial keratitis in southern California. A multivariate analysis. Ophthalmology 94 (10): 1322-1333. https://doi.org/10.1016/s0161-6420(87)80019-2

[13] Al-Mujaini A, Al-Kharusi N, Thakral A, Wali UK (2009) Bacterial keratitis: perspective on epidemiology, clinico-pathogenesis, diagnosis and treatment. Sultan Qaboos Univ Med J 9 (2): 184-195.

[14] Zagon IS, Sassani JW, Carroll MA, McLaughlin PJ (2010) Topical application of naltrexone facilitates reepithelialization of the cornea in diabetic rabbits. Brain Res Bull 81: 248–255. https://doi.org/10.1016/j.brainresbull.2009.10.009

[15] Kaji Y (2005) Prevention of diabetic keratopathy. Br J Ophthalmol 89 (3): 254-255. https://doi.org/10.1136/bjo.2004.055541

[16] Cisarik-Fredenburg P (2001) Discoveries in research on diabetic keratopathy. Optometry 72 (11): 691-704.

[17] Sánchez-Thorin JC (1998) The cornea in diabetes mellitus. Int Ophthalmol Clin 38 (2): 19-36.

[18] Schultz RO, Van Horn DL, Peters MA, Klewin KM, Schutten WH (1981) Diabetic keratopathy. Trans Am Ophthalmol Soc 79: 180-199.

[19] Ljubimov AV (2017) Diabetic complications in the cornea. Vision Res 139: 138-152. https://doi.org/10.1016/j.visres.2017.03.002

[20] Dyck PJ, Dyck PJB (1999) Diabetic polyneuropathy: section III. In: Dyck PJ, Thomas PK (ed) Diabetic Neuropathy, 2nd edn. Saunders, Philadelphia, pp. 255–278.

[21] Boulton AJ, Malik RA, Arezzo JC, Sosenko JM (2004) Diabetic somatic neuropathies. Diabetes Care 27 (6): 1458-1486. https://doi.org/10.2337/diacare.27.6.1458

[22] Zavoloka OV, Besditko PA, Lukhanin OO (2019) Efficacy of a novel non-contact corneal esthesiometer in assessing the neurotrophic status of the cornea in type I diabetic patients with bacterial keratitis. J Ophthalmol (Ukraine) 6: 29-33. http://doi.org/10.31288/oftalmolzh201962933

[23] Bikbova G, Oshitari T, Baba T, Bikbov M, Yamamoto S (2018) Diabetic corneal neuropathy: clinical perspectives. Clin Ophthalmol 25; 12: 981-987. https://doi.org/10.2147/OPTH.S145266

[24] Roszkowska AM, Licitra C, Tumminello G, Postorino EI, Colonna MR, Aragona P (2020) Corneal nerves in diabetes -The role of the in vivo corneal confocal microscopy of the subbasal nerve plexus in the assessment of peripheral small fiber neuropathy. Surv Ophthalmol 19: S0039-6257 (20) 30133-8. https://doi.org/10.1016/j.survophthal.2020.09.003

[25] Nielsen NV (1978) Corneal sensitivity and vibratory perception in diabetes mellitus. Acta Ophthalmol (Copenh) 56 (3): 406-411. https://doi.org/10.1111/j.1755-3768.1978.tb05693.x

[26] Rosenberg ME, Tervo TM, Immonen IJ, Müller LJ, Grönhagen-Riska C, Vesaluoma MH (2000) Corneal structure and sensitivity in type 1 diabetes mellitus. Invest Ophthalmol Vis Sci 41 (10): 2915-2921.

[27] Saito J, Enoki M, Hara M, Morishige N, Chikama T, Nishida T (2003) Correlation of corneal sensation, but not of basal or reflex tear secretion, with the stage of diabetic retinopathy. Cornea 22 (1): 15-18. https://doi.org/10.1097/00003226-200301000-00004

[28] Cousen P, Cackett P, Bennett H, Swa K, Dhillon B (2007) Tear production and corneal sensitivity in diabetes. J Diabetes Complications 21 (6): 371-373. https://doi.org/10.1016/j.jdiacomp.2006.05.008

[29] Tavakoli M, Kallinikos PA, Efron N, Boulton AJ, Malik RA (2007) Corneal sensitivity is reduced and relates to the severity of neuropathy in patients with diabetes. Diabetes Care 30 (7): 1895-1897. https://doi.org/10.2337/dc07-0175

[30] De Cillà S, Ranno S, Carini E, Fogagnolo P, Ceresara G, Orzalesi N, Rossetti LM (2009) Corneal subbasal nerves changes in patients with diabetic retinopathy: an in vivo confocal study. Invest Ophthalmol Vis Sci 50 (11): 5155-5158. https://doi.org/10.1167/iovs.09-3384

[31] Zhivov A, Winter K, Hovakimyan M, Peschel S, Harder V, Schober HC, Kundt G, Baltrusch S, Guthoff RF, Stachs O (2013) Imaging and quantification of subbasal nerve plexus in healthy volunteers and diabetic patients with or without retinopathy. PLoS One 8 (1): e52157. https://doi.org/10.1371/journal.pone.0052157

[32] Malik RA, Kallinikos P, Abbott CA, van Schie CH, Morgan P, Efron N, Boulton AJ (2003) Corneal confocal microscopy: a non-invasive surrogate of nerve fibre damage and repair in diabetic patients. Diabetologia 46 (5): 683-688. https://doi.org/10.1007/s00125-003-1086-8

[33] Kallinikos P, Berhanu M, O'Donnell C, Boulton AJ, Efron N, Malik RA (2004) Corneal nerve tortuosity in diabetic patients with neuropathy. Invest Ophthalmol Vis Sci 45 (2): 418-422. https://doi.org/10.1167/iovs.03-0637

[34] Mocan MC, Durukan I, Irkec M, Orhan M (2006) Morphologic alterations of both the stromal and subbasal nerves in the corneas of patients with diabetes. Cornea 25 (7): 769-773. https://doi.org/10.1097/01.ico.0000224640.58848.54

[35] Szalai E, Deák E, Módis L Jr, Németh G, Berta A, Nagy A, Felszeghy E, Káposzta R, Malik RA, Csutak A (2016) Early Corneal Cellular and Nerve Fiber Pathology in Young Patients With Type 1 Diabetes Mellitus Identified Using Corneal Confocal Microscopy. Invest Ophthalmol Vis Sci 57 (3): 853-858. https://doi.org/10.1167/iovs.15-18735