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Ocular bacterial flora and antimicrobial susceptibility profile of a diabetic population in Cameroon: an analytical study

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ABSTRACT

The ocular flora can be a contributing factor to potentially devastating eye infections, especially under certain conditions such as diabetes. The aim of this study was to determine the influence of diabetes on the bacterial conjunctival flora and to assess its susceptibility to antibiotics. In an analytical cross-sectional study conducted in three hospitals in the department of Ndé-Cameroon, we included diabetic and non-diabetic participants. Samples were obtained by swabbing the lower conjunctival fornix. Gram stain and culture were performed and antibiotic sensitivity determined in case of bacterial growth. A positive culture was found in 33/40 (82.5%) diabetic participants and 16/40 (40%) non-diabetic participants. Diabetic participants showed a more frequent positive flora for *Staphylococcus epidermidis*, *Bacillus*, and *Pseudomonas aeruginosa*, while the majority of non-diabetic patient's flora were *Bacillus*, *Staphylococcus epidermidis*, and *Staphylococcus saprophyticus*. In diabetics, resistance of *Staphylococcus Coagulase-negative* strains was observed in 80-100% of cases for Oxacillin and Trimethoprin-Sulfamethoxy. For Gram-negative strains, resistance was 80-100% for Penicillin, Oxacillin and Cefixime in diabetics. A positive culture was more frequently found in diabetic participants with a difference for the composition and antibiotic susceptibility compared to healthy people. This information may provide a better guideline for the prevention and the management of ocular diseases.

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Keywords: Diabetes, ocular flora, bacteria, susceptibility profile, *Staphylococcus*.

INTRODUCTION

Ophthalmic infections are a source of great eye morbidity. They can lead to visual impairment or even blindness, especially in high-risk groups and/or in cases of inappropriate care.

According to WHO, the spread of antibiotic resistance worldwide requires local and national action plans, as well as research

in building consensus on the prophylactic and curative use of antibiotics (WHO, 2015).

Studies on the profile of ocular flora pathogens and their susceptibility to antibiotics (Grzybowski et al., 2017; Sthapit and Tuladhar, 2014), and those involved in ocular infections (Miller, 2017; Sanfilippo et al., 2015), have been conducted worldwide. Thus, the most frequently found pathogens

were *Staphylococcus aureus* and coagulase-negative *Staphylococcus*.

Diabetes is a global public-health concern (Diabetes Atlas). It is likely to lead to visual impairment or even blindness because of its ocular complications, which may require surgical management.

People with diabetes, due to potential ocular complications, represent a group at risk of ocular infections. Cultures obtained from diabetic patients are more frequently positive (Grzybowski et al., 2017; Adam et al., 2015; Karimsab and Razak, 2013; El-Mollayess et al., 2012; Martins et al., 2004). Additionally, *Staphylococcus saprophyticus* remains the predominant pathogen in this population, with an increase of *Staphylococcus* found into cultures of patients with proliferative diabetic retinopathy (Karimsab and Razak, 2013; Martins et al., 2004). However, it is worth noting the paucity of existing data on ocular flora and their susceptibility to antibiotics, particularly in diabetics in our environment. However, according to Sanfilippo et al., the systematic determination of the microbial profile is essential because it leads to appropriate antibiotic use (Sanfilippo et al., 2015). Additionally, to combat low vision and even blindness, knowledge of the susceptibility of circulating pathogens would contribute to the development of a national consensus on the use of antibiotics.

The objective of our study was, therefore, to determine the influence of diabetes on the profile of the bacterial flora of the ocular conjunctiva and to evaluate its susceptibility to antibiotics. Since eye care professionals regularly provide various drugs for antibiotic prophylaxis in our context, such data could suggest the most appropriate prophylactic agents in diabetic patients.

MATERIALS AND METHODS

Site and participants

We conducted an analytical cross-sectional study in three hospitals in the Western region of Cameroon – namely Bafoussam Regional Hospital, Bangangté District Hospital, and Cliniques Universitaires des Montagnes for data collection. Biological

analysis of the samples was carried out at the Microbiology Laboratory of the Cliniques Universitaires des Montagnes. The study took place from July 1 to September 30, 2017. The research project was approved by the Ethics Committee of Université des Montagnes (N°/163/UdM/PR/CAB/CIE). After obtaining ethical clearance and administrative authorization, the work was carried out in strict compliance with the principles of the Helsinki Declaration.

The study included diabetic and non-diabetic participants who were free of eye infection, topical or systemic use of antibiotics and/or antifungals in the last two weeks before sampling, and of chronic use of eye drops. People with or without diabetes who had undergone ophthalmic surgery less than three months earlier were also excluded from the study. The sampling was consecutive.

Procedure

Participants underwent a comprehensive ophthalmologic examination to rule out the presence of an eye infection. Data on gender, age, and current general status were collected. Only one eye from each patient was randomly selected for the study. Samples were obtained by swabbing the lower conjunctival fornix with a sterile cotton swab, without touching the edges of the eyelids or eyelashes and without topical anesthesia.

In a laboratory, samples were incubated in a heart-brain broth at 37 °C. Turbidity of the milieu was observed until the seventh day. When the medium became turbid, agar culture by quadrant method and exhaustion was used. Otherwise, the sample was declared sterile. The agars used included Chapman, MacConkey, Colombia fresh blood, Colombia cooked blood, and Sabouraud. Gram staining was performed at the end of the incubation period and the smear obtained was examined with the X 100 objective of an optical microscope. A catalase test was, then, performed to distinguish *Staphylococcus* from *Streptococcus*. In addition to the morphological characteristics recorded on the agars after culture, other complementary tests, such as coagulase and DNAase tests, were

used to distinguish *Staphylococcus aureus* from other strains of *Staphylococcus* genus. For Gram-positive bacilli, identification was limited to morphological characteristics and a catalase test, while the identification process was further developed using Api10S galleries for Gram-negative bacilli.

Susceptibility tests were performed by disc diffusion (Kirby-Bauer), with conventional antibacterial agents commonly used in Cameroon. This was done with a pure 18-24 h bacterial culture grown on a nutrient agar. The test procedures and interpretations were carried out according to the standard guidelines recommended by the reference frame of reference "Comité de l'Antibiogramme de la Société Française de Microbiologie, CA-SFM, EUCAST, 2017".

Multidrug resistance was defined for strain resistance of 80% or more to a minimum of three antibiotics.

Statistical analysis

Data were saved in Microsoft Excel 2010 and exported to the Statistical Package for Social Sciences version 21 (IBM, Chicago, USA) for statistical analysis. Quantitative variables were expressed in numbers and percentages. Continuous variables were reported as mean \pm standard deviation. The comparison of mean age values was performed by the Student t-test. The qualitative variables were compared using Chi-square test and, for small samples, with the help of the exact Fischer test. P-values strictly less than 0.05 were considered statistically significant.

RESULTS

During the study period, 40 diabetic patients and 40 non-diabetic participants were included in the study, with a total of 80 participants.

Sociodemographic data

The mean age was 59 years + 16 years (extreme: 17-85 years) for diabetic participants and 29 years + 13 years (extreme: 11-77 years) for non-diabetics.

The population of diabetic participants consisted of 23 (57.50%) males and 17 (42.50%) females and the population of non-diabetics consisted of 17 (42.50%) males and 23 (57.50%) females.

Profile of the ocular flora

In total, a positive culture was found in 33/40 (82.5%) of diabetic participants and 16/40 (40%) of non-diabetics, representing 2.06 times more positive cultures in diabetics. The profile of bacteria found in diabetics and non-diabetics is summarized in Table 1.

Participants with diabetic status have a flora more frequently positive for *Staphylococcus epidermidis*, *Bacillus*, and *Pseudomonas aeruginosa*. In non-diabetics, *Bacillus*, *Staphylococcus epidermidis*, and *Staphylococcus saprophyticus* were the most frequently found pathogens.

Susceptibility of ocular flora pathogens to antibiotics

Antibiotic susceptibility was studied for coagulase negative *Staphylococcus* and Gram-negative *bacilli* and their results displayed in Tables 2 and 3 respectively.

As shown in Table 2, reduced susceptibility rates in coagulase negative *Staphylococcus* were obtained with some penicillins (penicillin: \leq 25%; Oxacillin: 0%) and third generation cephalosporins (ceftriaxone and ceftazidime) regardless of the patient's status. On the other hand, a high effectiveness was obtained with aminosides (gentamycin, Tobramycin) and an intermediate susceptibility rate with norfloxacin, a representative of the quinolone group (60%-62.5%).

In Table 3, reduced susceptibility rates in *Gram-negative bacilli* were obtained with Oxacillin (< 20%). Even though, a high effectiveness was obtained with Tobramycin regardless of the patient's status (> 80%), a reduced susceptibility rate was obtained with gentamycin, especially in non-diabetic participants. A low susceptibility rate was also obtained with vancomycin, particularly in non-diabetic participants (diabetic

participants: 50%; non-diabetic participants: 0%).

Antibiotic susceptibility of coagulase negative Staphylococcus

There is a difference in susceptibility for most antibiotics between the diabetic and non-diabetic populations.

In diabetics, resistance of strains was observed in 80-100% of cases for Oxacillin, Trimethoprin-Sulfamethoxy, Penicillin, and Ceftazidime. In non-diabetic patients, resistance was 80-100% for Oxacillin, Cefixime, and Ceftazidime. In both groups, the strains were multi-resistant.

Antibiotic susceptibility of pathogens Gram-negative bacilli

A difference in antibiotic susceptibility was observed between both groups with predominance in the non-diabetics.

In the diabetic patients' group, the resistance was 80-100% for Penicillin, Oxacillin and Cefixime. On the other hand, in the non-diabetic patients' group, resistance was 80-100% for Penicillin, Ampicillin, Oxacillin, Amoxicillin, Cefixime, Ceftazidime, Gentamycin, Vancomycin and Trimethoprin-Sulfamethoxy. In both groups, multi-resistant strains were observed.

Table 1: Profile of eye flora pathogens in diabetic participants and controls.

Designation	Diabetics (40) [n,%]	Non-diabetics (40) [n,%]	P-value
<i>Staphylococcus epidermidis</i>	14 (35,0)	4 (10,0)	0,007
<i>Staphylococcus saprophyticus</i>	5 (12,5)	4 (10,0)	0,720
<i>Staphylococcus aureus</i>	1 (2,5)	0 (0,0)	0,310
<i>Streptococcus-β-hémolytique</i>	0 (0,0)	1 (2,5)	0,310
<i>Morganella morganii</i>	1 (2,5)	0 (0,0)	0,310
<i>Bacillus</i>	11 (27,5)	6 (15,0)	0,170
<i>Pseudomonas aeruginosa</i>	7 (17,5)	0 (0,0)	0,006
<i>Pseudomonas fluorescens</i>	2 (5,0)	0 (0,0)	0,150
<i>Providencia stuarti</i>	1 (2,5)	0 (0,0)	0,310
<i>Weeksella virosa</i>	0 (0,0)	1 (2,5)	0,310
<i>Providencia alcalifaciens</i>	0 (0,0)	1 (2,5)	0,310
<i>Providencia rettgeri</i>	0 (0,0)	1 (2,5)	0,310
<i>Flavimonas oryzihaditans</i>	0 (0,0)	1 (2,5)	0,310

Table 2: Antibiotic susceptibility of Coagulase negative *Staphylococcus* in diabetic participants compared to non-diabetic participants.

Antibiotics	Diabetics		Non-diabetics		P-Value	
	Percentage of resistant strains (%)	Percentage of sensitive strains (%)	Percentage of resistant strains (%)	Percentage of sensitive strains (%)	Resistance (%)	Sensitivity (%)
Penicillin	87,5	12,5	50,0	25,0	0,01	0,25
Oxacillin	100	0,0	100	0,0	-	-
Amoxicillin	28,5	71,4	16,6	83,3	0,22	0,72
Amoxicillin+ Clavulanic acid	25	75	20,0	80,0	0,22	0,56
Ampicillin	28,5	71,4	0,0	100	0,05	0,42
Cephalotin	12,5	87,5	0,0	75,0	0,41	0,25
Cefoxitin	50	50,0	20,0	60,0	0,22	0,42
Cefuroxime	12,5	87,5	25,0	75,0	0,71	0,25
Cefixime	0,0	100	100	0,0	0,71	0,71
Cefotaxime	57,1	28,5	20,0	60,0	0,001	0,003
Ceftazidime	87,5	0,0	80,0	20,0	0,83	0,18
Ceftriaxone	50,0	0,0	20,0	40,0	0,27	0,05
Gentamycin	25,0	75,0	0,0	100	0,22	0,22
Tobramycin	25,0	75,0	20,0	80,0	0,11	0,11
Norfloxacin	37,5	62,5	20,0	60,0	0,50	0,50
Tetracycline	62,5	37,5	25,0	50,0	0,13	0,92
Vancomycin	37,5	50,0	50,0	50,0	0,92	0,72
Erythromycin	62,5	37,5	25,0	75,0	0,13	0,42
Chloramphenicol	25,0	75,0	0,0	100	0,22	0,22
Trimethoprine- sulfamethoxy	100	0,0	50,0	50,0	0,01	0,05
Rifampicin	14,2	85,7	0,0	100	0,41	0,22

Table 3: Antibiotic Susceptibility of Gram-negative Bacilli pathogens in diabetic Participants compared to non-diabetic participants.

Antibiotics	Diabetics		Non-diabetics		P-value Chi square test	
	Percentage of resistant strains (%)	Percentage of sensitive strains (%)	Percentage of resistant strains (%)	Percentage of sensitive strains (%)	Resistance (%)	Sensitivity (%)
Penicillin	100	0,0	100	0,0	-	-
Oxacillin	100	0,0	80	20,0	-	-
Amoxicillin	0,0	100	80	20,0	0,09	0,02
Amoxicillin+ Clavulanic acid	33,3	66,6	60,0	40,0	0,46	0,46
Ampicillin	0,0	100	100	0,0	0,005	0,03
Cephalotin	0,0	100	60,0	40,0	0,20	0,67
Cefoxitin	33,3	66,6	75,0	25,0	0,85	0,18
Cefuroxime	0,0	100	75,0	25,0	0,09	0,85
Cefixime	100	0,0	100	0,0	-	-
Cefotaxime	0,0	100	66,6	33,3	0,20	0,67
Ceftazidime	66,6	0,0	80,0	20,0	0,67	0,48
Keftriaxone	0,0	33,3	60,0	40,0	0,09	0,85
Gentamycin	33,3	66,6	80,0	20,0	0,16	0,16
Tobramycin	0,0	100	0,0	80,0	-	0,40
Norfloxacin	0,0	100	0,0	80,0	-	0,67
Tetracycline	0,0	100	0,0	100,0	-	-
Vancomycin	50,0	50,0	100,0	0,0	0,03	0,16
Erythromycin	33,3	66,6	60,0	40,0	0,46	0,46
Chloramphenicol	0,0	100,0	0,0	100,0	-	-
Trimethoprine- sulfamethoxy	0,0	100,0	100,0	0,0	0,005	0,03
Rifampicin	0,0	100,0	0,0	100,0	-	-

DISCUSSION

Diabetes is a public health problem responsible for multi-organic disorders, including eyes. This study determines the profile of the conjunctival flora and its antibiotic sensibility in diabetic patients compared to healthy ones. Diabetic participants (82.5%) had twice as many positive cultures as non-diabetic patients (40%). The high prevalence of bacterial growth can be explained by the alteration of immunity due to diabetes (Grzybowski et al., 2017; Adam et al., 2015; Karimsab and Razak, 2013; El-Mollayess et al., 2012; Martins et al., 2004). Others authors have reported that hyperglycemia and high-grade systemic inflammation in diabetic patients may promote the growth and colonization of potential pathogens (Li et al., 2019; Fernandez-Rubio et al., 2010). In the literature, the proportion and ratio of positive cultures of diabetic participants and controls varies among authors. Some authors have described significant proportions of positive cultures. Martins et al., reported 94.1% and 73.3% positive cultures in diabetics (n=103) and controls (n=60), respectively (Martins et al., 2004). Bilen et al. found 78.2% and 50% of positive cultures in diabetics (n=66) and controls (n=50), respectively (Bilen et al., 2007). On the other hand, lower rates of positive cultures are also described. Adam et al. reported rates of 38.5% and 34.9% for diabetics (n=53) and controls (n=43), respectively (Adam et al., 2015). Karimsab et al. reported 34.6% and 24% of positive cultures in diabetics (n=75) and controls (n=25), respectively (Karimsab and Razak, 2013). Additionally, according to Karimsab (2013) and Martins (2004), the rate of positive cultures was higher among diabetics with proliferating diabetic retinopathy (Karimsab and Razak, 2013; Martins et al., 2004).

In our series, coagulase-negative *Staphylococcus* was the most common bacteria, with *Staphylococcus epidermidis* and *Staphylococcus saprophyticus* at the top of the list in both diabetics and controls. Additionally, it should be noted that *Staphylococcus epidermidis* was statistically

more frequent in diabetic participants. Indeed, coagulase-negative *Staphylococcus* is part of the microbiota of human skin and mucous membranes (Becker et al., 2014). It is also known as a major component of the ocular flora in all populations around the world (Grzybowski et al., 2017; Sthapit and Tuladhar, 2014; Liu et al., 2011; Capriotti et al., 2009).

In several comparative studies, coagulase-negative *Staphylococcus* is strongly represented in cultures performed on diabetic eye samples (Karimsab and Razak, 2013; Martins et al., 2004; Bilen et al., 2007). Additionally, Martins et al. observed that coagulase-negative *Staphylococcus* was more frequently found in patients with proliferative diabetic retinopathy (Martins et al., 2004). On the other hand, other authors, such as Adam et al., have found coagulase-positive *Staphylococcus* as the majority pathogen (Adam et al., 2015).

For Gram-negative bacilli, *Bacillus* and *Pseudomonas aeruginosa* were more frequent in diabetic samples, while only *Bacillus* predominated in control samples. Gram-negative bacilli are also part of the human commensal flora (Grzybowski et al., 2017; Sthapit and Tuladhar, 2014; Liu et al., 2011; Capriotti et al., 2009). In our series, *Pseudomonas aeruginosa* was statistically more important among diabetic participants. This pathogen is known to be involved in most eye infections (Miller, 2017; Sanfillipo et al., 2015; Asbell et al., 2015).

Coagulase-negative *Staphylococcus* is recognized as a major nosocomial pathogen and is a challenge because of its resistant strains and its ability to produce a biofilm (Becker et al., 2014). A 100% oxacillin-resistance rate was found amongst both diabetic coagulase-negative *Staphylococcus* and non-diabetics' strains. In the literature, it has been recognized that oxacillin-resistant strains of coagulase-negative *Staphylococcus* are most often multi-resistant (Grzybowski et al., 2017; Sanfillipo et al., 2015; Becker et al., 2014). Our results are aligned with those found in the literature. Indeed, strains were found to be multi-resistant with high

resistance rates for Oxacillin, Penicillin, Trimethoprin-Sulfamethoxy, and Ceftazidime (80-100%) in the diabetic patients' group. Additionally, amongst our non-diabetic participants, a high-resistance rate was obtained for Oxacillin, Cefixime, and Ceftazidime (80-100%).

Antibiotic susceptibility

Vancomycin susceptibility of diabetic and non-diabetics coagulase-negative *Staphylococcus* strains was 50%. According to Asbell et al., vancomycin susceptibility was observed in all *Staphylococcus* strains collected in ocular infections (Asbell et al., 2015). Indeed, vancomycin and glycopeptides remain the preferred treatments for coagulase-positive *Staphylococcus* infections, especially for resistant-methicillin strains: although the decrease in susceptibility of coagulase-negative *Staphylococcus* strains has been described in the literature (Becker et al., 2014). The increase in vancomycin resistance in our context can also be explained by inappropriate antibiotic use and/or self-medication. However, approximately three quarters of coagulase-negative *Staphylococcus* strains showed sensitivity to several antibiotics from the penicillin family, such as Amoxicillin (diabetics: 71.4%; Controls: 83.3%), Ampicillin (diabetics: 71.4%; Controls: 100%), and Amoxicillin + Clavulanic acid (diabetics: 75%; Controls: 80%). Coagulase-negative *Staphylococcus* of both groups also showed susceptibility in more than 75% of cases for aminoglycosides (gentamycin and tobramycin) and for some cephalosporins (Cephalotin, Cefuroxime). According to the work of Kivanç, the high multidrug resistance rate of *Staphylococcus* isolated from ocular flora in their diabetic population was associated to its ability to produce biofilms (Kivanç et al., 2018). Therefore, molecules tested in our study may be used as a prophylactic and therapeutic arsenal in our setting even though the susceptibility profile should be monitored on a regular basis. Ngassam et al., in a study conducted in the same locations as ours (Bafoussam Regional Hospital, Bangangté

District Hospital, and Cliniques Universitaires des Montagnes) found a high contamination rate of isolates collected with a predominance of *Bacillus* and *Staphylococcus*. Susceptibility profiles also indicated high resistance rates (Ngassam et al., 2017).

Concerning Gram-negative bacilli strains, multidrug resistance at variable rates was observed in both groups with predominance in controls. However, good sensitivity of these strains was noted in both groups to Norfloxacin (diabetics: 100%; Controls: 80%), Tobramycin (diabetics: 100%; Controls: 80%), and Tetracycline (diabetics: 75%; Controls: 100%). Asbell et al., in the US ARMOR study of 3237 eye samples, found a low resistance rate of *Pseudomonas aeruginosa* strains (Asbell et al., 2015).

In contrast, in Europe, in a multi-center study of 741 eye samples, multi-resistance of Gram-negative bacilli strains, which varies from country to country, was observed (Sanfillipo et al., 2015). This raises the challenge of appropriate antibiotic use based on the systematic determination of pathogen susceptibility in ophthalmology. Moreover, the variability of antibiotic susceptibility also raises the issue of sensitization against antibiotic misuse and self-medication.

The limit of our work lies in the size of the sample. Additionally, the two groups were not matched in age in our series. Age appears to be a factor that may influence the profile of the bacterial flora. In fact, some researchers have reported a high prevalence of methicillin-resistant organisms in the elderly, particularly those over 60 years of age (Suto et al., 2012). However, there is controversy about the relationship between age and these methicillin-resistant bacteria (Hsu et al., 2015).

Regarding the determination of the susceptibility of strains to antibiotics, we have tried to test, as far as possible, the antibiotics used in ophthalmology. Additionally, strains tested could have been limited to those most involved with eye infection. However, this work provides us with important information about the diabetic population in our context.

Conclusion

The objective of this study was to determine the influence of diabetes on the bacterial flora of the ocular conjunctiva and to evaluate its susceptibility to antibiotics. At the end, it appeared that a positive culture was more frequently found in diabetic participants' flora, with a predominance of *Staphylococcus epidermidis*, *Bacillus*, and *Pseudomonas aeruginosa*. On the other hand, *Bacillus*, *Staphylococcus epidermidis* and *Staphylococcus saprophyticus* were the most frequently found pathogens amongst the non-diabetic patients.

A difference in susceptibility was observed for coagulase-negative *Staphylococcus* and Gram-negative bacilli for most antibiotics between the diabetic and non-diabetic populations. The strains were multi-resistant in both populations. The variability in antibiotic susceptibility and multidrug resistance raises the challenge of building a local consensus on antibiotic use in at-risk populations.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

All authors made a substantial contribution to the concept or design of the work; or acquisition, analysis or interpretation of data, drafted the article or revised it critically for important intellectual content, and approved the version to be published.

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