Contents lists available at ScienceDirect

Primary Care Diabetes

journal homepage: http://www.elsevier.com/locate/pcd

Original research

The association between diabetes, level of glycaemic control and eye infection: Cohort database study

*Abdus Samad Ansari**, *Simon de Lusignan*, *William Hinton*, *Neil Munro*, *Andrew McGovern*

Section of Clinical Medicine and Ageing, Department of Clinical and Experimental Medicine, University of Surrey, Guildford GU2 7PX, UK

ARTICLE INFO

Article history:
Received 5 March 2017
Received in revised form
26 May 2017
Accepted 26 May 2017
Available online 23 June 2017

Keywords:
Complications
Glycaemic control
Retinopathy
Eye infections
Conjunctivitis
Blepharitis
Endopthalmitis
Periorbital cellulitis

ABSTRACT

Aim: To examine whether diabetes and the degree of glycaemic control is associated with an increased risk of acute eye infection, and prescribing of ocular antimicrobial agents.
Design and setting: A retrospective cohort study was carried out using the Royal College of General Practitioners Research and Surveillance Centre database (RCGP RSC), a large primary care database in the United Kingdom. We compared ocular infection rates in people aged ≥15 years without diabetes to those with diabetes, both type 1 and type 2. We developed logistic regression models to assess the excess risk in diabetes of: conjunctivitis, blepharitis, stye/chalzion, periorbital cellulitis, keratitis/keratoconjunctivitis, lacrimal gland infection, endopthalmitis, and ocular antimicrobial prescriptions over a six-year period (2010–2015). We also analysed the impact of glycaemic control on infection rates in those with diabetes. All models were adjusted for potential confounders.
Results: We analysed infection risk in 889,856 people without diabetes and 48,584 people with diabetes (3273 type 1, and 45,311 type 2). After adjustment for confounders both type 1 and type 2 were associated with increased incidence of conjunctivitis (OR 1.61; 95% CI 1.38–1.88; $p < 0.0001$ and OR 1.11; 95% CI 1.06–1.16; $p < 0.0001$ respectively). No association was found with blepharitis, stye/chalzion, periorbital cellulitis, keratitis/keratoconjunctivitis, lacrimal gland infection, and endopthalmitis in the whole population. In subgroup analyses blepharitis was more common in those with type 1 diabetes under 50 years old and endopthalmitis in those under 50 with type 2 diabetes. Glycaemic control was not found to be associated with any infection. Diabetes was also associated with an increased incidence of antimicrobial prescriptions (Type 1 OR 1.69; 95% CI 1.51–1.88; $p < 0.0001$ and type 2 OR 1.17; 95% CI 1.13–1.20; $p < 0.0001$).
Conclusions: Conjunctivitis is recorded more frequently in people with diabetes. However, no substantial increase in recording of other ocular infections was noted. Infection risk was not found to be associated with the degree of glycaemic control.

* *Corresponding author.*
E-mail address: s.ansari@surrey.ac.uk (A.S. Ansari).
http://dx.doi.org/10.1016/j.pcd.2017.05.009

1. Introduction

Research into the ocular manifestations of diabetes has focused on management of diabetic retinopathy and maculopathy due to the risk of proliferative retinal disease leading to blindness [1]. Ocular infections however also pose a significant challenge for this population, affecting quality of life and contributing to a significant number of healthcare visits in both primary and secondary care [1].

Bacterial, fungal, and viral infections can affect a number of structures of the eyes. Infections of the eyelids, nasolacrimal duct, conjunctiva, corneal surface, and infectious keratitis have all been suggested to occur more frequently in people with diabetes [2–7]. However, there is a paucity of systematically collected data to support these assertions. There is even more uncertainty about the role of glycaemic control in ocular infection risk. A recent review of observational studies and clinical trials demonstrated a correlation between poor glycaemic control and increased risk of a wide variety of infections in people with diabetes [8]. This review identified only one small scale study ($n = 328$) carried out to determine the association between glycaemic control and superficial eye infections [9]. The authors found no significant relationship. Other studies have discussed poor glycaemic control as a possible risk factor for infectious conjunctivitis: conclusions have been limited by small sample size and limited measurements of glycaemic control [9,10].

Managing eye infections represents a significant health service workload despite the low morbidity of the conditions. Almost 1% of all primary care consultations are due to conjunctivitis [11,12], with more than five million episodes annually in the United States and 1 million in the United Kingdom [12]. Identification of modifiable risk factors for eye infections could therefore provide targets for reduction of this disease burden.

We explored whether infectious disease affecting the external eye and surrounding structures is associated with diabetes, and if poor glycaemic control increases risk of ocular infection in the population with diabetes. We hypothesised the following:

- People with diabetes have a higher frequency of ocular infections than those without diabetes.
- People with diabetes and poor glycaemic control have a higher number of ocular infections than those with diabetes and good glycaemic control.

2. Methods

We performed a two stranded study using data from the Royal College of General Practitioners Research and Surveillance Centre (RCGP RSC) database; a large UK based primary care cohort. The two study strands comprised; (1) a whole population cohort study to investigate the frequency of eye infections in people with diabetes compared to those without diabetes, and (2) a diabetes only population cohort study to investigate the impact of glycaemic control on eye infection rates in people with diabetes. We explored a wide range of infections of the eye and surrounding structures; conjunctivitis, blepharitis, stye/chalzion, periorbital cellulitis, keratitis/keratoconjunctivitis, lacrimal gland infection, endopthalmitis, ocular infection prescriptions, and all eye infections combined.

2.1. Data source

The RCGP RSC database comprises electronic patient records collated from a network of over 100 GP practices distributed across England containing over 1 million patient records. The characteristics of the RCGP-RSC population and participating practices have been recently described elsewhere [13]. Coded information for diagnostic, prescription, demographic and biochemical data is recorded in the database.

2.2. Study population and definition of variables

The study period for analysis of infection events was defined as the 5-year period between 1st January 2010 and 31st December 2015. All individuals aged ≥15 years who were registered with an RCGP RSC practice on 31st December 2015 were included for analysis. Patients in which the type of diabetes could not be determined were excluded from the analysis.

Clinical codes (Read version 2) and codes for medication use (EMIS codes in the RCGP RSC database) were used to determine patient characteristics and conditions, as these were the code types used by the participating practices. Diabetes was identified using recorded diabetes diagnosis codes, codes for diabetes clinical review, diabetes medication codes (oral hypoglycaemic agents, excluding metformin, and injectable agents), and laboratory results (two or more HbA1c values consistent with diabetes, or two or more blood glucose measurements consistent with diabetes, and depending on test provenance; fasting, random, glucose tolerance test, etc.) [14]. Other potential predictor variables for risk of eye infections were also extracted from coded data and included; age, gender, ethnicity, smoking status, body mass index (BMI), deprivation quintile, and the presence of connective tissue disorders. Age was defined as that at beginning of study period. Smoking status was categorised as current smoker, ex-smoker or never smoked and BMI as <18.5, 18.5–25, 25–30, and >30 kgm^{-2}. Ethnicity was categorised as Asian, Black, Mixed, White and other ethnic group, as per Office for National Statistics and Public Health England classification [15,16]. Where multiple values for the variable of interest were recorded the value nearest to the start of the follow up (1st January 2010) was used. Where information on the variable of interest was missing, people were categorised as 'not recorded' rather than excluded from the analysis. We have previously demonstrated that missing data can be correlated with outcomes in people with diabetes [17], and therefore this was our preferred approach to missing data.

Ocular infections investigated comprised conjunctivitis, blepharitis, stye/chalzion, periorbital cellulitis, keratitis/keratoconjunctivitis, lacrimal gland infection, and endopthalmitis. We also investigated the outcome measure of prescriptions for acute infectious ocular disease, all eye infections combined, and all eye infections excluding conjunctivitis (a post hoc group added during peer review). A final group

identified as miscellaneous infections was composed of infective episodes solely coded as 'eye infection' within patient notes. Results were also recorded for uveitis and scleritis, however, these were removed from the subsequent analysis, as we were unable to accurately differentiate between infective and non-infective disease. Blepharoconjunctivitis was removed from the study after no patients were found to have been clinically coded for this diagnosis. Codes relating to traumatic, chronic or non-infectious causes of disease were not included. A prescription for acute infectious ocular disease was defined as topical ocular antibiotics, antifungals, and antivirals. Corticosteroids and combination preparations of treatment were not included in prescriptions for acute infectious ocular disease.

2.3. *The association of diabetes with eye infections*

For this first component of the cohort study, infection rates in people with diabetes were compared to those without. Each infection variable was categorised as a binary outcome; i.e. it either occurred in the follow-up period or not, and as a categorical count variable; did not occur, occurred once, occurred twice, or occurred three or more times. Regression models were constructed to identify any association with diabetes and each infection type; logistic regression where a binary outcome was used and ordinal regression in the case of the categorical count outcomes. Potential confounders included in the regression analyses were: age, gender, ethnicity, deprivation quintile, body mass index (BMI), the presence of connective tissue disorders, and diabetes type (type 1 or type 2). In response to suggestions made during peer review we also performed a subgroup analysis comparing infection rates in those without diabetes to those with diabetes in the under 50 and 50 and over age groups. This analysis was suggested to investigate differential associations between diabetes, eye infections, and age group.

The association between glycaemic control and eye infection risk in people with diabetes

In this second component of the study only the cohort subset of people with diabetes were analysed to identify the impact of glycaemic control on infection rates. Two measures of glycaemic control were utilised to search for an association, each derived from HbA1c measurements:

(1) Single HbA1c measurement closest to the start of follow-up (1st January 2010)
(2) Area under the HbA1c curve (H_{AUC}) during the follow-up period:

$$H_{AUC} = \frac{\sum_{n=0}^{N} t_n \frac{H_n + H_{n+1}}{2}}{\sum_{n=0}^{N} t_n}$$

where N = total number of HbA1c measurements in the observation period ($n = 0$ to N), Hn = HbA1c value at time n, t_n = time between H_n and H_{n+1}. This approach is based on that of Maple-Brown et al. [18]

HbA1c levels were stratified as good (<53 mmol/mol (<7%)), moderate (53–68 mmol/mol (7–8.4%)), poor (69–100 mmol/mol (8.5–11.3%)), and very poor (>100 mmol/mol (>11.3%)). We have previously demonstrated that these strata described the association between glycaemic control and infection prevalence with a range of common infections [19]. Other variables examined included age, gender, ethnicity, smoking status, BMI, diagnosis of connective tissue disorder, the stage and diagnosis of retinopathy and presence of maculopathy. Retinopathy

Table 1 – The characteristics of the 938,440 people included in the study.

Characteristic	People without diabetes ($N = 889,856$) n (%)	People with diabetes ($N = 48,584$) n (%)
Age		
15–30	237,507 (26.7)	1175 (2.4)
30–45	242,706 (27.3)	4018 (8.3)
45–60	202,340 (22.7)	11,307 (23.3)
60–75	135,580 (15.2)	18,539 (38.2)
75+	71,723 (8.1)	13,545 (27.9)
Gender		
Men	432,950 (48.7)	26,756 (55.1)
Woman	456,906 (51.3)	21,828 (44.9)
Ethnicity		
Asian	37,864 (4.3)	3355 (6.9)
Black	23,747 (2.7)	1747 (3.6)
Mixed	7514 (0.8)	364 (0.7)
White	528,614 (59.4)	35,191 (72.4)
Other	8186 (0.9)	330 (0.7)
Not recorded	283,931 (31.9)	7597 (15.6)
Smoking		
Ex-smoker	220,240 (24.8)	12,052 (24.8)
Active	55,970 (6.3)	3047 (6.3)
Never	152,210 (17.1)	8326 (17.1)
Not recorded	461,436 (51.9)	25,159 (51.8)
BMI		
<18.5	16,377 (1.8)	385 (0.8)
18.5–25	221,438 (24.9)	8298 (17.1)
25–30	166,334 (18.7)	16,076 (33.1)
>30	104,646 (11.8)	21,424 (44.1)
Not recorded	381,061 (42.8)	2401 (4.9)
Connective tissue disorders	8384 (0.9)	1212 (2.5)
Deprivation quintile		
1	150,330 (16.9)	9074 (18.7)
2	150,948 (17.0)	8765 (18.0)
3	152,684 (17.2)	8317 (17.1)
4	190,408 (21.4)	10,327 (21.3)
5	234,914 (26.4)	11,842 (24.4)
Diabetes type		
Type1	–	3273 (6.7)
Type2	–	45,311 (93.3)
Diabetic retinopathy		
None	–	13,742 (28.3)
Non specific	–	19,070 (39.3)
Background	–	13,088 (26.9)
Pre-proliferative	–	1596 (3.3)
Proliferative	–	1088 (2.2)
Maculopathy	–	2949 (6.1)
HbA1c: mmol/mol (%)		
Good: <53 (7%)	–	16,950 (34.9)
Moderate: 54–69 (7–8.4%)	–	15,768 (32.5)
Poor: 70–100 (8.5–11.3%)	–	7225 (14.9)
Very Poor: >100 (>11.3%)	–	747 (1.5)
Not measured	–	7894 (16.2)

Table 2 – The number of people with one or more eye infection (by type) between 1st January 2010 and 31st December 2015 in 890,150 people without diabetes and 48,584 people with diabetes.

	No diabetes (N = 889,856)		Diabetes (N = 48,584)		p Value
	n	% (95% CI)	n	% (95% CI)	
Conjunctivitis	39,245	4.410 (4.375–4.446)	3321	6.836 (6.648–7.025)	<0.0001
Blepharitis	14,390	1.617 (1.595–1.639)	1365	2.810 (2.686–2.933)	<0.0001
Stye/chalzion	18,160	2.041 (2.016–2.066)	1046	2.153 (2.046–2.262)	0.0922
Periorbital cellulitis	609	0.068 (0.064–0.073)	33	0.068 (0.049–0.089)	0.9657
Keratitis	356	0.040 (0.037–0.043)	32	0.066 (0.047–0.086)	0.0063
Lacrimal gland infections	267	0.030 (0.027–0.033)	24	0.049 (0.033–0.066)	0.0181
Endopthalmitis	52	0.006 (0.004–0.007)	15	0.031 (0.019–0.045)	<0.0001
Prescriptions	87,667	9.852 (9.800–9.904)	7956	16.376 (16.100–16.652)	<0.0001
Antimicrobial Prescription	26,470	2.975 (2.945–3.004)	2357	4.851 (4.691–5.012)	<0.0001
Conjunctivitis Prescriptions	14,871	1.671 (1.649–1.694)	1301	2.678 (2.558–2.799)	<0.0001
Total infections	65,852	7.400 (0.161–0.175)	5200	10.703 (10.473–10.934)	<0.0001
Total infections and prescriptions	103,094	11.585 (7.355–7.446)	8802	18.117 (17.831–18.405)	<0.0001

was categorised as none, non-specific changes recorded, pre-proliferative, and proliferative. Maculopathy was categorised as present or absent.

2.4. *Statistical analysis*

Data was analysed using the R environment for statistical computing (R version 3.2.5). Infections and prescription episodes attested as outcome variables in both binary forms and as categorical counts for all models. We produced regression models for each individual infection type, prescription episodes, and an overall cumulative infection and prescription models. Age, BMI, and HbA1c were all stratified within levels as described above. Where no cases of infection were identified in strata or group for an included variable then no odds ratio (OR) is reported for the category. For example, we found no cases of endopthalmitis in people with type 1 diabetes; we therefore do not report an OR for this group. Adjusted ORs and 95% confidence intervals are reported with associated p values. Associations were considered significant if they were associated with a p value, corrected for multiple testing (from a single test significance level $p < 0.05$) using the Bonferroni-Šidák equation [20]. For the association of infections with diabetes (20 tests) this equated to significance at $p < 0.00256$ and for the association with glycaemic control in diabetes (40 tests) and subgroup analyses by age (40 tests) at $p < 0.00128$. Since all infections combined excluding conjunctivitis was a post hoc addition made during peer review this is not included in the number of tests used to calculated these adjusted p values.

3. Results

3.1. *Patient characteristics*

A total of 939,028 people aged ≥15 years were available for inclusion in the study. People were excluded if their type of diabetes could not be determined ($n = 588$). A final population of 938,440 people was included in the study. Approximately half of the population (432,950; 48.7%) were men. 48,584 (5.2%) people had diabetes; type 1 (3273; 6.7%) and type 2 (45,311, 93.3%). The characteristics of people without diabetes and with diabetes are shown in Table 1.

During the follow-up period we identified a total of 65,852 (7.0%) people who had one or more eye infections. These included: conjunctivitis ($n = 39,245$ episodes), blepharitis ($n = 14,390$), stye/chalzion ($n = 18,160$), periorbital cellulitis ($n = 609$), infectious keratitis/keratoconjunctivitis ($n = 356$), lacrimal gland infection ($n = 267$), endopthalmitis ($n = 52$), and non-category specific eye infections ($n = 1494$). 87,667 people had one or more prescriptions for ocular infections. We also identified 2528 people with uveitis and 1483 people with scleritis. These events were not included in subsequent analyses due to a high likelihood of chronic or non-infectious causes. A comparison of the number of infection events in people without and with diabetes is shown in Table 2.

3.2. *The association of diabetes with eye infections*

Logistic regression models for infections demonstrated an association between diabetes and conjunctivitis, blepharitis (type 1 only), endopthalmitis (type 2 only), prescriptions for topical antimicrobial agents, all infections combined, and infections and prescriptions combined (Table 3A and B). No association was found between stye/chalzion, periorbital cellulitis, keratitis/keratoconjunctivitis, and lacrimal gland infection and diabetes. When correcting significance at a level for multiple testing ($p < 0.00256$), only the associations between diabetes and conjunctivitis, prescriptions, all infections combined, and infections and prescriptions combined remained significant. No patients were found to have type 1 diabetes and endopthalmitis. The odds ratio for conjunctivitis was higher in type 1 diabetes compared to type 2. Complete models with odds ratios for confounder variables are provided in the Appendix. Categorical regression analyses also demonstrated a relationship between diabetes and conjunctivitis but not with other infections.

Subgroup analysis explored comparisons between diabetes, infection and age group (under and over 50 years of age) (Table5A and B). In the under 50 population we identified correlations between conjunctivitis (Type 1 and 2), blepharitis (type 1), endopthalmitis (Type 2), prescriptions (type 1 and 2), infections and prescriptions (type 1 and 2), all infections combined (type 1 and 2) and all infections excluding conjunctivitis (type

2). Conversely in the population above 50 such associations were not seen apart from prescriptions (type 1 only).

3.3. *The association between glycaemic control and eye infection risk in people with diabetes*

We found no significant association between infection risk and glycaemic control (using the area under the curve method) for any of the infection types analysed, after adjusting for potential confounders, and using a p value for significance adjusted for multiple testing ($p < 0.00128$) (Table 4A and B). We also generated logistic regression models for each infection using a single HbA1c measurement prior to follow up, and similarly no association with infection incidence was identified. In addition, we repeated these analyses using ordinal regression analyses to look for associations between glycaemic control and the number of infections during the follow-up period, and found no significant associations.

No infection cases were found for; endopthalmitis in people with a diagnosis of preproliferative retinopathy, periorbital cellulitis with an HbA1c >100 mmol/mol, infectious keratitis and preproliferative disease and lacrimal gland and HbA1c >100 or proliferative disease.

4. Discussion

Conjunctivitis was found to occur more frequently in people with diabetes but incidence was not related to the degree of glycaemic control. We found no significant relationship between diabetes and blepharitis, stye/chalzion, periorbital cellulitis, keratitis/keratoconjunctivitis, lacrimal gland infection, and endopthalmitis. There was association with all infections combined and both type 1 and type 2 diabetes although this was lost when conjunctivitis was excluded. Prescriptions for ocular antimicrobial agents were more common in people with diabetes, which maybe partly redirected by the increased incidence of conjunctivitis. Other possibilities may be, that this is in part, explained by an increased propensity to consult and to prescribe in this population or by eye infections lasting longer or translating to more severe forms in those with diabetes.

Subgroup analyses suggest a possible increased incidence of blepharitis in those with type 1 under 50 and endopthalmitis in those with type 2 diabetes under 50 after adjusting for multiple testing. All infections excluding conjunctivitis were also more common in those with type 2 diabetes under 50 although the implications of this are unclear from these data. Despite adjustment for multiple testing these findings of subgroup analyses should be treated with caution and explored further in a separate population. Our results are reassuring in that no substantially increased risk for most eye infections could be detected in people with diabetes in this large population. However, there may be an increased risk for certain infections in younger patients with diabetes.

4.1. *Limitations and strengths of the method*

The strengths of our study include the large population size and the high quality of routine data collection pro-

Table 3A and B – Odds ratios for one or more eye infections (by type) between 1st January 2010 and 31st December 2015 in 890,150 people without diabetes and 48,584 people with diabetes. Models adjusted for age, gender, ethnicity, deprivation quintile, body mass index (BMI), and the presence of connective tissue disorders. No diabetes used as reference in regression models. P value for significance (corrected for multiple testing): <0.00256.

Diabetes type	Conjunctivitis		Blepharitis		Stye/Chalzion		Periorbital Cellulitis		Infectious Keratitis/ Keratoconjunctivitis	
	Odds ratio (95% CI)	p Value	Odds ratio (95% CI)	p Value	Odds ratio (95% CI)	p Value	Odds ratio (95% CI)	p Value	Odds ratio (95% CI)	p Value
Type 1	1.61 (1.38–1.88)	<0.0001	1.39 (1.06–1.83)	0.0184	1.13 (0.88–1.45)	0.3458	0.59 (0.08–4.19)	0.5962	2.80 (0.89–8.79)	0.0770
Type 2	1.11 (1.06–1.16)	<0.0001	1.04 (0.97–1.11)	0.2944	1.00 (0.92–1.07)	0.9354	0.89 (0.59–1.34)	0.5723	1.11 (0.72–1.72)	0.6226

Diabetes type	Lacrimal Gland Infection		Endopthalmitis		Prescriptions		Infections and prescriptions		All infections combined		All infections excluding conjunctivitis	
	Odds ratio (95% CI)	p Value	Odds ratio (95% CI)	p Value	Odds ratio (95% CI)	p Value	Odds ratio (95% CI)	p Value	Odds ratio (95% CI)	p Value	Odds ratio (95% CI)	p Value
Type 1	1.45 (0.20–10.40)	0.7105	No cases	–	1.69 (1.51–1.88)	<0.0001	1.60 (1.44–1.77)	<0.0001	1.44 (1.27–1.64)	<0.0001	1.19 (1.44–0.98)	0.0844
Type 2	1.12 (0.69–1.84)	0.6449	2.81 (1.40–5.62)	0.0036	1.17 (1.13–1.20)	<0.0001	1.15 (1.11–1.18)	<0.0001	1.08 (1.04–1.12)	<0.0001	1.03 (1.08–0.98)	0.3241

Table 4A and B – The odds ratios for infection incidence in 48,584 people with diabetes stratified by glycaemic control. Models are adjusted for age, gender, ethnicity, body mass index (BMI), the presence of connective tissue disorders, the degree of retinopathy and the presence of maculopathy. *p* Value for significance (corrected for multiple testing): <0.00128.

Variables	Conjunctivitis		Blepharitis		Stye/Chalzion		Periorbital cellulitis		Keratitis	
	Odds ratio (95% CI)	*p* Value	Odds ratio (95% CI)	*p* Value	Odds ratio (95% CI)	*p* Value	Odds ratio (95% CI)	*p* Value	Odds ratio (95% CI)	*p* Value
HbA1c (mmol/mol)										
<53 (Ref) (*n* = 16,950)	1	–	1	–	1	–	1	–	1	–
53–69 (*n* = 15,768)	1.05 (0.96–1.15)	0.2861	1.09 (0.95–1.24)	0.2172	0.94 (0.81–1.10)	0.4535	0.77 (0.29–2.05)	0.6083	0.86 (0.36–2.04)	0.7253
69–100 (*n* = 7225)	1.06 (0.94–1.19)	0.3645	0.95 (0.79–1.15)	0.6208	0.93 (0.76–1.13)	0.4703	3.04 (1.22–7.54)	0.0168	0.83 (0.27–2.53)	0.7499
>100 (*n* = 747)	0.90 (0.65–1.24)	0.5201	0.76 (0.42–1.37)	0.3558	0.74 (0.43–1.29)	0.2916	No cases		1.47 (0.17–12.49)	0.7226
Not measured (*n* = 7984)	0.39 (0.33–0.46)	<0.0001	0.42 (0.32–0.55)	<0.0001	0.37 (0.27–0.51)	<0.0001	No cases		0.49 (0.09–2.55)	0.3928
Retinopathy										
None (Ref) (*n* = 13,742)	1	–	1	–	1	–	1	–	1	–
Background (*n* = 13,088)	1.00 (0.89–1.13)	0.9898	1.16 (0.97–1.40)	0.1100	1.24 (1.00–1.53)	0.0505	2.93 (0.35–24.55)	0.3217	1.28 (0.38–4.27)	0.6912
Non-specific (*n* = 19,070)	0.98 (0.88–1.10)	0.7455	1.13 (0.96–1.35)	0.1512	1.14 (0.93–1.39)	0.2024	6.57 (0.87–49.31)	0.0672	1.42 (0.47–4.33)	0.5331
Preproliferative (*n* = 1596)	1.39 (1.13–1.72)	0.0019	1.53 (1.11–2.09)	0.0088	1.34 (0.91–1.96)	0.1359	6.84 (0.57–82.05)	0.1292	No cases	
Proliferative (*n* = 1088)	1.23 (0.95–1.58)	0.1174	1.25 (0.83–1.87)	0.2839	1.02 (0.63–1.65)	0.9339	4.95 (0.29–84.58)	0.2696	1.25 (0.12–12.86)	0.8534
Maculopathy (*n* = 2949)	1.00 (0.85–1.18)	0.9853	1.24 (0.99–1.57)	0.0667	0.94 (0.71–1.25)	0.6672	0.81 (0.17–3.97)	0.7958	1.17 (0.25–5.49)	0.8466

Variables	Lacrimal gland infection		Endopthalmitis		All infective episodes		All prescriptions		All infections and prescriptions	
	Odds ratio (95% CI)	*p* Value	Odds ratio (95% CI)	*p* Value	Odds ratio (95% CI)	*p* Value	Odds ratio (95% CI)	*p* Value	Odds ratio (95% CI)	*p* Value
HbA1c (mmol/mol)										
<53 (Ref) (*n* = 16,950)	1	–	1	–	1	–	1	–		
53–69 (*n* = 15,768)	0.28 (0.09–0.88)	0.0297	0.93 (0.20–4.25)	0.9248	1.01 (0.94–1.08)	0.8557	1.05 (0.99–1.12)	0.0899	1.04 (0.98–1.10)	0.2237
69–100 (*n* = 7225)	0.29 (0.06–1.36)	0.1158	2.39 (0.54–10.56)	0.2518	1.00 (0.91–1.11)	0.9326	1.11 (1.02–1.20)	0.0109	1.09 (1.00–1.17)	0.0370
>100 (*n* = 747)	No cases		7.82 (1.10–55.80)	0.0403	0.83 (0.64–1.09)	0.1797	0.92 (0.74–1.15)	0.4763	0.89 (0.71–1.10)	0.2674
Not measured (*n* = 7984)	0.33 (0.06–1.66)	0.1781	0.63 (0.10–3.85)	0.6181	0.40 (0.35–0.46)	<0.0001	0.43 (0.38–0.48)	<0.0001	0.42 (0.38–0.47)	<0.0001
Retinopathy										
None (Ref) (*n* = 13,742)	1	–	1	–	1	–	1	–	1	–
Background (*n* = 13,088)	0.74 (0.21–2.67)	0.6468	0.17 (0.03–1.00)	0.0498	1.07 (0.97–1.18)	0.1646	1.10 (1.02–1.20)	0.0188	1.11 (1.03–1.20)	0.0078
Non-specific (*n* = 19,070)	0.72 (0.23–2.26)	0.5759	0.47 (0.13–1.68)	0.2436	1.04 (0.95–1.14)	0.3874	1.12 (1.03–1.20)	0.0046	1.11 (1.03–1.19)	0.0069
Preproliferative (*n* = 1596)	4.28 (0.84–21.86)	0.0808	No cases		1.42 (1.19–1.69)	<0.0001	1.41 (1.22–1.64)	<0.0001	1.42 (1.23–1.64)	<0.0001
Proliferative (*n* = 1088)	No cases		0.61 (0.08–4.73)	0.6388	1.23 (0.99–1.52)	0.0575	1.32 (1.10–1.58)	0.0022	1.37 (1.15–1.62)	0.0003
Maculopathy (*n* = 2949)	1.21 (0.23–6.34)	0.8228	6.76 (1.55–29.42)	0.0109	1.07 (0.94–1.22)	0.2814	1.12 (1.01–1.26)	0.0373	1.11 (1.00–1.24)	0.0532

Table 5A and B – Odds ratios for one or more eye infections (by type) between 1st January 2010 and 31st December 2015 separated into those below the age of 50 and above. Models adjusted for age, gender, ethnicity, deprivation quintile, body mass index (BMI), and the presence of connective tissue disorders. No diabetes used as reference in regression models. *p* Value for significance (corrected for multiple testing): <0.00128.

Age	Diabetes type	Conjunctivitis		Blepharitis		Stye/Chalzion		Periorbital cellulitis		Infectious Keratitis/ Keratoconjunctivitis	
		Odds ratio (95% CI)	p Value	Odds ratio (95% CI)	*p* Value	Odds ratio (95% CI)	*p* Value	Odds ratio (95% CI)	*p* Value	Odds ratio (95% CI)	*p* Value
Under 50	Type 1	1.80 (1.49–2.18)	<0.0001	1.83 (1.27–2.63)	0.0012	1.23 (0.91–1.65)	0.1855	0.85 (0.12–6.06)	0.8688	5.28 (1.66–16.80)	0.0048
	Type 2	1.53 (1.35–1.72)	<0.0001	1.36 (1.08–1.73)	0.0095	1.19 (1.00–1.42)	0.0541	0.49 (0.12–2.02)	0.3268	3.41 (1.42–8.20)	0.0060
Over 50	Type 1	1.30 (1.00–1.71)	0.0532	1.07 (0.70–1.62)	0.7566	0.97 (0.60–1.54)	0.8832	No cases	–	No cases	–
	Type 2	1.06 (1.01–1.11)	0.0150	1.00 (0.94–1.08)	0.8913	0.97 (0.89–1.06)	0.5133	0.93 (0.60–1.45)	0.7448	0.88 (0.54–1.44)	0.6215

Age	Diabetes type	Lacrimal Gland Infection		Endopthalmitis		Prescriptions		Infections and prescriptions		All infections combined		All infections excluding conjunctivitis	
		Odds ratio (95% CI)	*p* Value	Odds ratio (95% CI)	*p* Value	Odds ratio (95% CI)	*p* Value	Odds ratio (95% CI)	*p* Value	Odds ratio (95% CI)	*p* Value	Odds ratio (95% CI)	*p* Value
Under 50	Type 1	No cases	–	No cases	–	1.74 (1.37–2.21)	<0.0001	1.77 (1.55–2.01)	<0.0001	1.60 (1.37–1.88)	<0.0001	1.34 (1.71–1.05)	0.0175
	Type 2	No Cases	–	41.62 (5.32–325.78)	0.0004	1.43 (1.23–1.67)	<0.0001	1.46 (1.35–1.59)	<0.0001	1.41 (1.28–1.56)	<0.0001	1.25 (1.45–1.09)	0.0018
Over 50	Type 1	3.06 (0.42–22.03)	0.2674	No cases	–	1.70 (1.28–2.26)	0.0002	1.35 (1.13–1.61)	0.0010	1.20 (0.96–1.50)	0.1043	1.00 (1.38–0.72)	0.9897
	Type 2	1.07 (0.63–1.84)	0.8000	2.24 (1.08–4.64)	0.0300	1.08 (1.02–1.14)	0.0096	1.10 (1.07–1.13)	<0.0001	1.04 (1.00–1.08)	0.0628	1.00 (1.06–0.95)	0.9954

vided by the RCGP RSC practice network [13] Limitations of our study include those of any retrospective observational study: in particular, we cannot exclude residual confounding, and are unable to demonstrate causal relationships. In addition, despite the large population size there were small numbers of cases of infectious keratitis/keratoconjunctivitis, lacrimal gland infections, and endopthalmitis that may have limited our ability to identify associations. Cases involving stye/chalzion and infectious keratitis/keratoconjunctivitis were grouped by anatomy and one must appreciate these are clinically different infections. There is also a high likelihood that many patients do not seek medical help for common ocular infections such as conjunctivitis and styes/chalzion. Particularly as people are able to buy treatment over the counter. These infection events are therefore not recorded. Inclusion of other risk factors for acute ocular infection such as use of contact lenses [21], hygiene, or infection contact was not possible, as this data is not routinely recorded in UK primary care. Diabetes duration has also been independently associated with both increased risk of microvascular events [22] and infection [23], combined with our inability to highlight type of therapy; one must also appreciate this to be a limitation difficult for us to control for. Finally the severity of eye infections could not be determined from our dataset. This was due to the difficulty in defining a universally accepted classification system that would encompass the various infection forms. This was due to the varied structures of the eyes involved and the lack of information in routinely collected data.

4.2. *Comparison with the literature*

We found a lack of robust data examining the relationship between diabetes and infections despite multiple allusions to an association in the literature [6,7]. A population based case-control study in Denmark identified 502 people with diabetes and acute conjunctivitis (using prescribing records) in a total case population of 16,193 [10]. The odds ratio for conjunctivitis in those with diabetes compared to those without was OR 1.24 (95% CI 1.13–1.38). A smaller observational study ($n = 328$) of people with type 2 diabetes found no association between glycaemic control and acute conjunctivitis [9]. They hoped to establish a change in glycaemic control between periods of infection and without. Of the 458 infections studied, there were 26 cases of superficial infections of the eye (conjunctivitis & blepharitis). They found no change in HbA1c levels between episodes of infection and without [9]. Other authors have suggested recurrent styes, blepharitis and blepharoconjunctivitis all as possible indicators for undiagnosed diabetes and suggested diabetes screening in such patients [5]. Our data do not support this suggestion. To the best of our knowledge there are no other high quality studies that examine this these associations. Secondary care data has demonstrated an increased risk for postoperative endopthalmitis in those with diabetes [24]. The number of people with endopthalmitis in our cohort may have been too small to capture this association. Whilst we did identify a potential association with type 2 diabetes this was not significant after adjusting p values for multiple testing.

The pathogenesis relating to diabetes and ocular infections remains poorly understood. A number of studies in vivo and in vitro have demonstrated a hyperglycaemic state damages

the functionality of neutrophils and macrophages, in particular chemotaxis and phagocytosis [25]. However, the clinical implications are still inadequately understood. The conjunctival flora of people with and without diabetes is significantly different, with higher rates of culture positive for potentially pathogenic organisms in those with diabetes [26]. It has been suggested that this prevalence of conjunctival colonisation with pathogenic bacteria in patients with diabetes may be due to repeated hospital visits and recurrent antimicrobial therapy [27]. Reduced corneal sensitivity in people with diabetes may also play a role in increased risk for ocular infection; the sensory deficit potentially predisposing patients to bacterial, corneal and neurotropic ulcers [10].

5. Conclusions

This is the first large study to examine the association between diabetes and a range of eye infections in a large population. We found that conjunctivitis occurs more frequently in people with diabetes, however, we did not find any substantial increase in risk for other ocular infections. For rarer infections we cannot exclude an association due to small numbers. Infection risk was not found to be associated with the degree of glycaemic control. Hyperglycaemia does not appear to be a major predisposing factor to ocular infections.

Author contributions

ASA, Sdel and AMcG were involved in the conception and design of the study. ASA, AMcG, WH and BA were involved in data collection. ASA and AMcG carried out the statistical analysis and data interpretation. ASA drafted the manuscript. ASA, AMcG, Sdel, WH, BA and NM provided critical review of the manuscript and contributed to the final write-up. AMcG was the senior study investigator. All authors read and approved the final manuscript.

Role of funding source

This study has no funding source or sponsor to be reported.

Conflicts of interest

ASA has no conflicts of interest to declare. AMG, WH, BA and SdL have undertaken research funded by Eli-Lilly. NM has received fees for serving as a speaker, a consultant or an advisory board member for Allergan, Bristol-Myers Squibb-Astra-Zeneca, GlaxoSmithKline, Eli Lilly, Lifescan, MSD, Metronic, Novartis, Novo Nordisk, Pfizer, Sankio, Sanofi, Roche, Servier, Takeda.

Acknowledgements

We would like to thank Mrs Barbara Arrowsmith for her assistance in data extraction for this study.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.pcd.2017.05.009.

REFERENCES

[1] E.W. Gregg, N. Sattar, M.K. Ali, The changing face of diabetes complications, Lancet Diabetes Endocrinol. 4 (6) (2016) 537–547.
[2] M. Bharathi, R. Ramakrishnan, S. Vasu, R. Meenakshi, R. Palaniappan, Epidemiological characteristics and laboratory diagnosis of fungal keratitis. A three-year study, Indian J. Ophthalmol. 51 (4) (2003) 315–321.
[3] U. Gopinathan, P. Garg, M. Fernandes, S. Sharma, S. Athmanathan, G.N. Rao, The epidemiological features and laboratory results of fungal keratitis: a 10-year review at a referral eye care center in South India, Cornea 21 (6) (2002) 555–559.
[4] E.C. Alfonso, D. Miller, J. Cantu-Dibildox, T.P. O'Brien, O.D. Schein, Fungal keratitis associated with non-therapeutic soft contact lenses, Am. J. Ophthalmol. 142 (1) (2006) 154–155.
[5] A. Negi, S.A. Vernon, An overview of the eye in diabetes, J. R. Soc. Med. 96 (6) (2003) 266–272.
[6] P.R. Herse, A review of manifestations of diabetes mellitus in the anterior eye and cornea, Am. J. Optom. Physiol. Opt. 65 (3) (1988) 224–230.
[7] G. Rocha, G. Garza, R.L. Font, Orbital pathology associated with diabetes mellitus, Int. Ophthalmol. Clin. 38 (2) (1998) 169–179.
[8] J. Pearson-Stuttard, S. Blundell, T. Harris, D.G. Cook, J. Critchley, Diabetes and infection: assessing the association with glycaemic control in population-based studies, Lancet Diabetes Endocrinol. 4 (2) (2016) 148–158.
[9] M.L. Bartelink, L. Hoek, J.P. Freriks, G.E. Rutten, Infections in patients with type 2 diabetes in general practice, Diabetes Res. Clin. Pract. 40 (1) (1998) 15–19.
[10] A. Kruse, R.W. Thomsen, H.H. Hundborg, L.L. Knudsen, H.T. Sorensen, H.C. Schonheyder, Diabetes and risk of acute infectious conjunctivitis—a population-based case-control study, Diabet. Med. 23 (4) (2006) 393–397.
[11] J.K. Dart, Eye disease at a community health centre, Br. Med. J. (Clin. Res. Ed.) 293 (6560) (1986) 1477–1480.
[12] Royal College of General P, A. McCormick, D. Fleming, J. Charlton, B. Great, C. Office of Population, et al., Morbidity Statistics from General Practice: Fourth National Study 1991–1992, H.M.S.O., London, 1995.
[13] A. Correa, W. Hinton, A. McGovern, J. van Vlymen, I. Yonova, S. Jones, et al., Royal College of General Practitioners Research and Surveillance Centre (RCGP RSC) sentinel network: a cohort profile, BMJ Open 6 (4) (2016).
[14] A.P. McGovern, H. Fieldhouse, Z. Tippu, S. Jones, N. Munro, S. de Lusignan, Glucose test provenance recording in UK primary care: was that fasted or random? Diabet. Med. (2016).
[15] Government DfCaL, English Indices of Deprivation 2015. English Indices of Deprivation, 2015.
[16] Statistics OfN, Poverty, Wealth and Social Security – National Statistics, UK Data Service, 2015.
[17] A.P. McGovern, B. Rusholme, S. Jones, J.N. van Vlymen, H. Liyanage, H. Gallagher, et al., Association of chronic kidney disease (CKD) and failure to monitor renal function with adverse outcomes in people with diabetes: a primary care cohort study, BMC Nephrol. 14 (1) (2013) 1–11.

[18] L.J. Maple-Brown, C. Ye, R. Retnakaran, Area-under-the-HbA1c-curve above the normal range and the prediction of microvascular outcomes: an analysis of data from the Diabetes Control and Complications Trial, Diabet. Med. 30 (1) (2013) 95–99.
[19] J.L. Hine, S. de Lusignan, D. Burleigh, S. Pathirannehelage, A. McGovern, P. Gatenby, et al., Association between glycaemic control and common infections in people with Type 2 diabetes: a cohort study, Diabet. Med. (2016).
[20] O.J. Dunn, Multiple comparisons among means, J. Am. Stat. Assoc. 56 (293) (1961) 52–64.
[21] C. Cochrane, Contact lenses and bacterial infections, Nurs. Stand. 7 (20) (1993) 32–34 (Royal College of Nursing (Great Britain): 1987).
[22] S. Zoungas, M. Woodward, Q. Li, M.E. Cooper, P. Hamet, S. Harrap, et al., Impact of age, age at diagnosis and duration of diabetes on the risk of macrovascular and microvascular complications and death in type 2 diabetes, Diabetologia 57 (12) (2014) 2465–2474.
[23] J.R. Simonsen, V. Harjutsalo, A. Järvinen, J. Kirveskari, C. Forsblom, P.-H. Groop, et al., Bacterial infections in patients with type 1 diabetes: a 14-year follow-up study, BMJ Open Diabetes Res. Care 3 (1) (2015).
[24] W.B. Phillips 2nd, W.S. Tasman, Postoperative endophthalmitis in association with diabetes mellitus, Ophthalmology 101 (3) (1994) 508–518.
[25] M. Delamaire, D. Maugendre, M. Moreno, M.C. Le Goff, H. Allannic, B. Genetet, Impaired leucocyte functions in diabetic patients, Diabet. Med. 14 (1) (1997) 29–34.
[26] H. Bilen, O. Ates, N. Astam, H. Uslu, G. Akcay, O. Baykal, Conjunctival flora in patients with type 1 or type 2 diabetes mellitus, Adv. Ther. 24 (5) (2007) 1028–1035.
[27] M.E. Fernandez-Rubio, T. Cuesta-Rodriguez, J.L. Urcelay-Segura, C. Cortes-Valdes, Pathogenic conjunctival bacteria associated with systemic co-morbidities of patients undergoing cataract surgery, Eye 27 (8) (2013) 915–923.