Journal of Diabetes and Its Complications xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: www.jdcjournal.com

# Glycemic control is an important modifiable risk factor for uveitis in patients with diabetes: A retrospective cohort study establishing clinical risk and ophthalmic disease burden

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ARTICLE INFO

*Article history:*
Received 20 September 2017
Received in revised form 4 March 2018
Accepted 17 March 2018
Available online xxxx

*Keywords:*
Uveitis
Scleritis
Glycaemic control
Hba1c
Episcleritis
Retinopathy

ABSTRACT

*Aim:* To characterize the risk uveitis, scleritis or episcleritis in relation to diabetes, glycaemic control, and co-existence of retinopathy.
*Methods:* Using the Royal College of General Practitioners Research and Surveillance Centre database, we established the prevalence of acute uveitis and scleritis or episcleritis over a six-year period among populations without($n = 889,856$) and with diabetes($n = 48,584$). We evaluated the impact of glycaemic control on disease risk. Regression modeling was used to identify associations, adjusting for clinical and demographic confounders.
*Results:* Incidence of acute uveitis was higher among patients with diabetes; Type 1 OR:2.01 (95% CI 1.18–3.41; $p = 0.009$), and Type 2 OR:1.23 (1.05–1.44; $p = 0.01$). Glycaemic control was established as an important effect modifier for uveitis risk, whereby those with poorer control suffered higher disease burden. Results confirmed a dose-response relationship such that very poor glycaemic control OR:4.72 (2.58–8.65; $p < 0.001$), poor control OR:1.57 (1.05–2.33; $p = 0.03$) and moderate control OR:1.20 (0.86–1.68; $p = 0.29$) were predictive of uveitis. Similar results were observed when evaluating retinopathy staging: proliferative retinopathy OR:2.42 (1.25–4.69; $p = 0.01$). These results were not maintained for scleritis or episcleritis.
*Conclusion:* Acute uveitis is more common in patients with diabetes; at highest risk are those with type 1 disease with poor glycaemic control. Glycaemic improvements may prevent recurrence.


## 1. Introduction

Uveitis, scleritis and diabetes are individual risk factors for blindness. Diabetes is the third most common cause of blindness in the western world,[1] and the most common cause of blindness in those of working age.[2] Posterior uveitis is the fifth most common cause of blindness in industrialised nations.[1,3] Uveitis involves intraocular inflammation and is categorised by its location anatomically, duration and by its multifactorial aetiology. It is commonly classified into infectious and non-infectious forms, and by the orientation of the inflammation, implicit to the uveal tract of the intraocular environment. Anterior uveitis is the most prevalent,[4] with idiopathic aetiologies being encountered more so than the infectious. Although the vast majority of clinical and functional outcomes among this cohort of patient remain good, severe forms of disease can have catastrophic implications on a patient's sight.[3]

Scleritis involves the inflammation of the sclera and present with a painful red eye with or without visual loss, much like uveitis its aetiology is multifactorial, often linked to systemic autoimmune disease and is classified by location of inflammation around the globe (anterior or posterior) and type of disease (necrotizing/non-necrotizing: diffuse/nodular). It has been shown to cause vision loss (a permanent drop in Snellen acuity of two or more lines) in 9% of patients with diffuse anterior disease, 26% in patients with nodular scleritis, 74% in those with necrotizing disease and 84% in those with posterior scleritis.[5] Most cases are managed empirically with the use of anti-inflammatory therapy,[6] with little consideration given to prevention apart from posterior forms of scleritis due to its potential for acute sight loss.

Episcleritis, however is a benign self-limiting inflammatory disease that affects the episclera commonly managed without complications. It can cause a diagnostic challenge at times to differentiate between the disease and scleritis, with initial clinical features of the two diseases shown to be very similar.[7] Patients present with discomfort and localised injection. It is classified into two forms, simple and nodular with severe forms of disease requiring topical steroids.

Poor glycaemic control in diabetes has been associated with an increased risk of microvascular, macrovascular and infectious complications.[8,9] It is diabetic retinopathy and maculopathy that are responsible for the visual impairment in this group. Of an estimated 285 million people with diabetic retinopathy worldwide, one third have retinal microvascular complications, and in a third of this population the complications threaten vision.[10]

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https://doi.org/10.1016/j.jdiacomp.2018.03.008
1056-8727/

Individually, these conditions may have a profound effect on an individual's capacity to see, and when a patient presents with more than one condition together the effect can often lead to accelerated,[11] irreversible impairment to the patient's vision and can provide a clinical challenge to manage in both primary and secondary care. We explored whether acute presentations of uveitis and scleritis or episcleritis were associated with diabetes and attempted to investigate if glycaemic control influenced risk of occurrence. It has long been suggested that there is a relationship between type 1 diabetes and uveitis and a potential association with poor glycaemic control, however a recent review[12] found no large scale studies assessing these relationships. The authors concluded that the association between diabetes and uveitis is contentious and requires further research.[12] There is an even great paucity of data on any potential relationship with type 2 diabetes,[12] and to our knowledge no research has established whether diabetes type holds additional prognostic value for predicting uveitis risk. Given these outstanding questions we feel that the data from our large-scale cohort study (despite the limitations of such studies) still provides a significant addition to the existing literature.

We hypothesised:

- The diabetic population would have a higher frequency of acute episodes of disease in comparison to the general population
- People with diabetes and poor glycaemic control would be more prone to risk of acute disease in comparison to patients with better glycaemic control

## 2. Methods

Utilising the Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) database we performed a retrospective cohort study with a nested investigation of glycaemic control and of pre-existing retinopathy in people with diabetes. The RCGP RSC database is made up of UK primary care data, this data source lends itself to this type of study because practices have been computerised since the late 1990s and there is a registration-based system with one patient registered with a single practice. Care is free at the point of delivery.

Our retrospective cohort study analysed the frequency of these inflammatory diseases in the population with diabetes in comparison to those without diabetes. The nested study investigated those with diabetes to evaluate what, if any, association existed between glycaemic control and episodes of acute uveitis and scleritis. The nested study incorporated data for stage of retinopathy and maculopathy; due to its already well-documented relationship to glycaemic control.[13]

### 2.1. Data source

The characteristics of the RCGP-RSC population and participating practices has been described elsewhere.[14,15] The electronic database contains information on over 1 million patients assembled from over 100 GP practices across England. Information is coded by participating practices for biochemical, prescription, diagnostic and demographic data into computerised medical record (CMR) systems as part of routine care.[16] Data within the RCGP RSC database is extracted from primary care records. In the UK patients are only able to register with a single GP practice. The results of any secondary care encounters, such as contact with an ophthalmologist are reported to the patients' GP in written letters and any new diagnoses are coded into their primary care record.

### 2.2. Study population and the definition of variables

A six-year study period was defined between the dates of 1st of January 2010 and 31st December 2015. All patients fully registered with an RCGP RSC general practice and aged ≥15 were included for analysis, we did not include temporary residents. We excluded patients from analysis when we could not establish the type of diabetes.

Structured data were extracted to ascertain patient information in relation to the demographics, conditions and biochemical data. Coded disease data were recoded by all participating practices using the Read classification.[17] Diabetes was identified using codes for recoded diagnosis, diabetes clinical review, diabetic medication (including oral hypoglycaemic agents, excluding metformin and agents commonly injected by this cohort) and the use of laboratory results. We have a well-established approach to validating diabetes diagnoses.[18,19] This consisted of two or more HbA1c values identified to be consistent with a diagnosis of diabetes and depending on test provenance; fasting, random, glucose tolerance test.[20]

Other variables that could potentially influence prediction on acute episode were also extracted from the coded database. This included patient age, gender, deprivation quintile, ethnicity, body mass index (BMI) and presence of connective tissue disorder. These were defined as following:

- Age: At the start of the study period (1st January 2010), only those 15 years old and older were included
- Gender: Male or female
- Deprivation Quintile: 1 to 5 as measured using the Index of Multiple Deprivation the National official measure defined by Public Health England and used by the National office of Statistics.[21]
- Ethnicity: Asian, Black, Mixed, White or Other ethnic group (categories as defined by the Office for National Statistics and Public Health England).[22]
- BMI: categorised as <18·5, 18·5 to 25, 25 to 30, and >30 kg $m^{-2}$
- Connective tissue disorder: Underlying diagnosis made prior to, or during study period: present or absent.

Acute ocular disease investigated included uveitis and scleritis or episcleritis. Due to the nature of coding in primary care, scleritis and episcleritis were grouped together for the purposes of our analysis. We were unable to differentiate between infective and non-infectious causes, and thus all results were included in our study. Codes that related to traumatic, or chronic causes were excluded from our study. Medications were not used to identify disease, as we felt the medication used to treat these diseases were primarily started in secondary care and was not reliable due to the broad application of use.

### 2.3. Diabetes and its relationship to acute uveitis and scleritis or episcleritis

In our retrospective cohort study we compared the occurrence of acute episodes in people with diabetes in comparison to those without. Individual episodes of disease were categorised as a binary outcome (whether they occurred; yes or no) and as a categorical outcome (whether they did not occur, occurred once, twice and so on). We utilised logistic regression models when looking at the relationship between diabetes and individual disease and ordinal regression in cases involving categorical count outcomes. Confounders that were included in our models included: age, gender, ethnicity, deprivation quintile, body mass index (BMI), diagnosis of connective tissue disorder and type of diabetes (type 1 or 2).

### 2.4. Glycaemic control and its association to acute uveitis and scleritis or episcleritis

The nested study only involved people with diabetes. We aimed to analyse the influence of glycaemic control on acute episodes of uveitis and scleritis or episcleritis and to investigate if there was any additional influence of the stage of retinopathy. We used two different measures of glycaemic control to determine association. We used: (1) The single HbA1c measure found to closest to the start of our study period; and (2) Measurements of HbA1c calculated from the areas under the curve, over the whole study period, an approach based on that of Maple-Brown et al.[23] We found that the choice of HbA1c did not

Please cite this article as: Ansari AS, et al. Glycemic control is an important modifiable risk factor for uveitis in patients with diabetes: A retrospective cohort study establ.... (2018), https://doi.org/10.1016/j.jdiacomp.2018.03.008

significantly impact our findings and therefore we report our findings using the area under the curve (Table 2).

The equation used was:

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

$N$ number of hbA1c measurements in totality during the observation period.
$H_n$ HbA1c value at time $n$,
$t_n$ time between $H_n$ and $H_{n+1}$

HbA1c results we initially included as a linear variable in our regression models, however we found that the relationship between HbA1c and uveitis was non-linear. HbA1c results were subsequently stratified as good (<7% (<53 mmol/mol)) moderate (7–8.4%(53–68 mmol/mol)), poor (8.5–11.3% (69–100 mmol/mol)) and very poor (>11.3% (>100 mmol/mol)). We have previously demonstrated that these strata helpfully categorise the association between glycaemic control and infection prevalence in a number of systemic infections[24] and more recently ocular infections.[9] Other variables included within the nested element of the study, included: age, gender, ethnicity, BMI, diagnosis of connective tissue disorder, stage and diagnosis of retinopathy and diagnosis of maculopathy.

Retinopathy was categorised as per national screening guidelines: none, non-specific, background, pre-proliferative and proliferative.[25] Maculopathy was categorised as present or absent.

### 2.5. Statistical analysis

We utilised R Version 3.2.5 for data analysis. Acute episodes were corroborated to outcome variables. This was done in both binary and categorical counts for all the models created. Individual regression models were created to look at acute uveitis and scleritis. In instances where no cases of disease were identified for a specific variable category we did not report an Odds Ratio (OR) for that variable category. Subsequently adjusted ORs and 95% confidence intervals were reported with their associated $p$-value. Results were deemed significant if they were associated with a p-value significance level of <0.05.

**Table 1**
Patient characteristics.

| Demographic | Without a diagnosis of diabetes (N = 889,856) | Diagnosis of diabetes (N = 48,584) |
|---|---|---|
| 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 | | |
| Male | 432,950 (48.7%) | 26,756 (55.1%) |
| Female | 456,906 (51.3%) | 21,828 (44.9%) |
| Connective tissue disorders | 8384 (0.9%) | 1212 (2.5%) |
| Type of diabetes | | |
| 1 | – | 3273 (6.7%) |
| 2 | – | 45,311 (93.3%) |
| Stage of diabetic retinopathy | | |
| None | – | 13,742 (28.3%) |
| Nonspecific | – | 19,070 (39.3%) |
| Background | – | 13,088 (26.9%) |
| Preproliferative | – | 1596 (3.3%) |
| Proliferative | – | 1088 (2.2%) |
| Presence of maculopathy | – | 2949 (6.1%) |
| HbA1c %(mmol/mol) | | |
| <7%(<53) (ref) | – | 16,950 (34.9) |
| 7%–8.4%(53–69) | – | 15,768 (32.5) |
| 8.5%–11.3%(69–100) | – | 7225 (14.9) |
| >11.3%(>100) | – | 747 (1.5) |
| Unknown | – | 7894 (16.2) |

The summarised demography of the 938,440 people included in the study: including age, gender, connective tissue disorder, stage of retinopathy and HbA1c.

### 2.6. Ethical considerations

This study was classified by the Medical Research Council (MRC) Health Research Authority (HRA) tool as a Service Evaluation and the study was also approved by the RCGP study review processes reference: RSC_2617.

## 3. Results

### 3.1. Patient characteristics

939,028 people were available to be included in our study. People were excluded if we were unable to define the type of diabetes ($n$ = 588) or were aged <15 years. This provided us with a final total population of 938,440. Of these patients 48,584 were identified to have diabetes: Type 1 ($n$ = 3273) and Type 2 ($N$ = 45,311). A full description of our patient characteristics have been published elsewhere, (a brief summarised form is noted in Table 1).[26] During the follow up period we identified a total of 4011 episodes of acute uveitis or scleritis or episcleritis in the entire population, which consisted of: acute uveitis ($n$ = 2528) and scleritis or episcleritis ($n$ = 1483). Within the diabetic cohort we identified a total of 334 total episodes of disease: uveitis ($n$ = 253) and scleritis or episcleritis ($n$ = 81).

### 3.2. The association between diabetes, acute uveitis and scleritis or episcleritis

Utilising logistic regression models we completed an initial analysis on the entire population (Table 2). We identified that the risk of an episode of acute uveitis to increase with age, with the highest risk seen in those aged between 60 and 75 years. Acute uveitis was found to occur more commonly in the Asian and Black population with no significant variation noted when patients were stratified by socioeconomic deprivation or BMI. Acute uveitis was significantly more common in people with type 1 diabetes and type 2 diabetes, than in those without diabetes after adjusting for confounders.

Conversely scleritis or episcleritis was found to occur least commonly in patients aged between 15 and 30 or over the age of 75. No variation was identified by ethnicity however increased episode risk was found to be associated with socioeconomic deprivation quintiles 4 and 5 (the most deprived groups). No such relationship was identified between diabetes and scleritis or episcleritis.

### 3.3. The association between glycaemic control acute uveitis and scleritis or episcleritis

Within the diabetes cohort we did not find any association with acute uveitis and age, sex or socioeconomic deprivation; however we did note increased episode occurrence risk in those from Asian and Black ethnic backgrounds (Table 3). We identified an increased risk of disease with worsening glycaemic control with the greatest risk seen in those with an HbA1c >11.3% (>100 mmol/mol). There was no relationship with retinopathy other than an increased risk in those with a diagnosis of proliferative disease. Fig. 1 displays the odds ratios derived from the multi-variable logistic regression, illustrating the magnitude of effect of modifiable risk factors included in the model (HbA1c and retinopathy categories). We find HbA1c (>11.3%) and proliferative retinopathy are most predictive of uveitis. We also see HbA1c maintains a dose-response relationship for predicting uveitis, whereby the predictive risk for uveitis increases according to the severity of glycaemic control (Fig. 1).

Whilst males appeared to have fewer episodes of scleritis or episcleritis, no statistically significant relationship was identified with

**Table 2**
Entire study population model results.

| Variables | Acute uveitis | | Scleritis or Episcleritis | |
|---|---|---|---|---|
| | Odds ratio (95% CI) | *p* value | Odds ratio (95% CI) | *p* value |
| Age | | | | |
| 15–30 | 0.53 (0.44–0.63) | $p < 0.0001$ | 0.39 (0.32–0.48) | $p < 0.0001$ |
| 30–45 (ref) | 1 | – | 1 | – |
| 45–60 | 1.65 (1.45–1.88) | $p < 0.0001$ | 1.13 (0.97–1.31) | $p = 0.1123$ |
| 60–75 | 1.97 (1.72–2.26) | $p < 0.0001$ | 0.95 (0.80–1.13) | $p = 0.5848$ |
| 75+ | 1.54 (1.29–1.83) | $p < 0.0001$ | 0.45 (0.34–0.59) | $p < 0.0001$ |
| Gender | | | | |
| Male | 1.02 (0.93–1.11) | $p = 0.7456$ | 0.56 (0.50–0.64) | $p < 0.0001$ |
| Ethnicity | | | | |
| Asian | 1.65 (1.38–1.97) | $p < 0.0001$ | 1.24 (0.97–1.59) | $p = 0.0815$ |
| Black | 2.17 (1.79–2.64) | $p < 0.0001$ | 1.18 (0.86–1.62) | $p = 0.3146$ |
| Mixed | 1.74 (1.19–2.53) | $p = 0.0040$ | 1.09 (0.62–1.93) | $p = 0.7679$ |
| White (ref) | 1 | – | 1 | – |
| Other | 0.90 (0.54–1.50) | $p = 0.6777$ | 0.73 (0.36–1.47) | $p = 0.3739$ |
| BMI | | | | |
| <18.5 | 0.83 (0.54–1.26) | $p = 0.3785$ | 0.46 (0.23–0.93) | $p = 0.0302$ |
| 18.5 ≥ 24.9 (ref) | 1 | – | 1 | – |
| 25 ≥ 29.9 | 1.00 (0.88–1.14) | $p = 0.9993$ | 1.14 (0.96–1.35) | $p = 0.1239$ |
| ≥30 | 1.22 (1.06–1.40) | $p = 0.0046$ | 1.18 (0.99–1.42) | $p = 0.0712$ |
| None | 1.03 (0.91–1.17) | $p = 0.6320$ | 1.01 (0.86–1.18) | $p = 0.9504$ |
| Deprivation quintile | | | | |
| 1 (ref) | 1 | – | 1 | – |
| 2 | 1.08 (0.92–1.27) | $p = 0.3235$ | 0.90 (0.71–1.14) | $p = 0.3731$ |
| 3 | 1.22 (1.04–1.42) | $p = 0.0151$ | 1.31 (1.05–1.62) | $p = 0.0162$ |
| 4 | 1.14 (0.97–1.32) | $p = 0.1058$ | 1.49 (1.21–1.83) | $p = 0.0001$ |
| 5 | 1.20 (1.03–1.39) | $p = 0.0172$ | 1.64 (1.35–1.99) | $p < 0.0001$ |
| Connective tissue disorders | 1.94 (1.47–2.56) | $p < 0.0001$ | 3.04 (2.21–4.18) | $p < 0.0001$ |
| Diabetes | | | | |
| No diabetes (ref) | 1 | – | 1 | – |
| Type 1 | 2.01 (1.18–3.41) | $p = 0.0099$ | 1.08 (0.45–2.60) | $p = 0.8687$ |
| Type 2 | 1.23 (1.05–1.44) | $p = 0.0098$ | 0.84 (0.64–1.10) | $p = 0.2087$ |

Results from regression models looking at diabetes as a variable for acute uveitis and scleritis or episcleritis. Models adjusted for gender, age, ethnicity, deprivation quintile, BMI and diagnosis of connective tissue disorder.

age, ethnicity, glycaemic control, retinopathy, and maculopathy or socioeconomic deprivation quintile within the diabetic population (Table 2).

## 4. Discussion

Our results found episodes of acute uveitis to occur more frequently in people with diabetes, particularly in those with type 1 disease. Prevalence had a linear association with worse glycaemic control. No significant relationship was found between scleritis or episcleritis, diabetes, glycaemic control, retinopathy or maculopathy.

Our study is the first large population study to clearly demonstrate the relationship of glycaemic control on the prevalence of acute uveitis, whilst simultaneously confirming its relationship to microvascular complications frequently seen in those with poor control. Although scleritis, episclertis and uveitis can be multifactorial in aetiology, our results would suggest different pathological processes that influence recurrent episodes of disease, particularly in people with diabetes. Our results suggest that glycaemic control could be a major modifiable risk factor in preventing the occurrence and recurrence of acute uveitis in people with diabetes.

### *4.1. Limitations and strengths of our study*

The primary strengths of our study include the population size and the high quality of routine data collection that is provided by the RCGP RSC practice network. We have been able to look at several associations over a long period of time. Our population size is also larger than any study looking at these associations to date. Limitations include those of any retrospective database observational study. This includes our inability to exclude residual confounding; we were unable to demonstrate causal relationships. Additionally due to either infrequency of disease on a whole, or poor transfer of recording from secondary care to primary care, our population size ideally would be increased to better identify associations. Due to data quality limitations and numbers, we decided to group together the various forms of each disease that are generally separated into anatomical site and aetiology. This hindered are ability to differentiate between scleritis and episcleritis. Primary care coding practices at present, commonly code these two clinically varied diseases together. In optimal conditions sub categorized forms of uveitis, scleritis and episcleritis should be studied.

Uveitis, we would have liked to classify into anterior, posterior, intermediate, panuveitis and scleritis into anterior, posterior, nodular, and necrotizing and Episcleritis into its simple and nodular forms. However these were poorly differentiated in primary care data. We would also have liked to investigate the diseases aetiologically to see if idiopathic forms of disease varied in comparison to infectious or autoimmune associated presentations, but again this data was limited and poorly recorded.

There is also a possibility that a number of patients are incorrectly or not coded onto primary care systems leading to missed episodes of disease we are unable to identify. There is also a large population that directly presents to secondary care, and whilst these encounters are routinely communicated to the patients GP in primary care, information transfer inevitably leads to missed cases and recording bias. We were also unable to look at a number of patient important and clinical outcomes including visual acuity, intraocular pressure and clinical presentation findings which are usually recorded in free text in the record and not available for researchers; all of which would be useful in better understanding this relationship. Finally it must also be noted that the ratio of scleritis/episcleritis to uveitis cases may indeed seem higher than noted in practice by many ophthalmologists. We feel that this is

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**Table 3**
Diabetic population models.

| Variables | Acute uveitis | | Scleritis or episcleritis | |
|---|---|---|---|---|
| | Odds ratio (95% CI) | p value | Odds ratio (95% CI) | p value |
| Age: | | | | |
| 15–30 | 1.51 (0.61–3.73) | $p = 0.3673$ | 0.81 (0.09–6.98) | $p = 0.8473$ |
| 30–45 (ref) | 1 | – | 1 | – |
| 45–60 | 1.46 (0.84–2.55) | $p = 0.1774$ | 1.44 (0.54–3.81) | $p = 0.4679$ |
| 60–75 | 1.29 (0.74–2.26) | $p = 0.3681$ | 0.99 (0.38–2.63) | $p = 0.9895$ |
| 75+ | 1.42 (0.79–2.55) | $p = 0.2463$ | 0.51 (0.17–1.55) | $p = 0.2359$ |
| Gender | | | | |
| Male | 0.96 (0.73–1.27) | $p = 0.7879$ | 0.45 (0.27–0.75) | $p = 0.0020$ |
| Ethnicity | | | | |
| Asian | 2.09 (1.40–3.11) | $p = 0.0003$ | 1.66 (0.80–3.45) | $p = 0.1729$ |
| Black | 2.17 (1.24–3.79) | $p = 0.0063$ | 0.80 (0.19–3.39) | $p = 0.7629$ |
| Mixed | 1.91 (0.60–6.06) | $p = 0.2712$ | 3.24 (0.78–13.55) | $p = 0.1071$ |
| White (ref) | 1 | – | 1 | – |
| Other | 2.38 (0.74–7.59) | $p = 0.1440$ | No cases | No cases |
| Deprivation quintile | | | | |
| 1 (ref) | 1 | – | 1 | – |
| 2 | 1.51 (0.94–2.42) | $p = 0.0874$ | 1.23 (0.54–2.80) | $p = 0.6234$ |
| 3 | 1.86 (1.17–2.96) | $p = 0.0084$ | 0.92 (0.38–2.23) | $p = 0.8480$ |
| 4 | 1.54 (0.95–2.48) | $p = 0.0781$ | 0.79 (0.32–1.96) | $p = 0.6164$ |
| 5 | 1.75 (1.11–2.76) | $p = 0.0157$ | 1.79 (0.85–3.74) | $p = 0.1241$ |
| Connective tissue disorders | 1.04 (0.42–2.54) | $p = 0.9332$ | 4.10 (1.74–9.68) | $p = 0.0013$ |
| Retinopathy | | | | |
| None (ref) | 1 | – | 1 | – |
| Background | 0.89 (0.57–1.41) | p = 0.6234 | 2.03 (0.89–4.65) | $p = 0.0944$ |
| Non-specific | 1.18 (0.78–1.78) | $p = 0.4357$ | 1.27 (0.56–2.89) | $p = 0.5744$ |
| Preproliferative | 1.68 (0.87–3.24) | $p = 0.1218$ | 1.07 (0.21–5.50) | $p = 0.9314$ |
| Proliferative | 2.42 (1.25–4.69) | $p = 0.0089$ | 1.68 (0.33–8.59) | $p = 0.5323$ |
| Maculopathy | 1.15 (0.71–1.87) | $p = 0.5661$ | 1.50 (0.63–3.54) | $p = 0.3592$ |
| HbA1c %(mmol/mol) | | | | |
| <7% (<53) (ref) | 1 | – | 1 | – |
| 7%–8.4% (53–69) | 1.20 (0.86–1.68) | $p = 0.2932$ | 1.07 (0.61–1.87) | $p = 0.8177$ |
| 8.5%–11.3% (69–100) | 1.57 (1.05–2.33) | $p = 0.0269$ | 0.89 (0.42–1.89) | $p = 0.7669$ |
| >11.3% (>100) | 4.72 (2.58–8.65) | $p < 0.0001$ | No Cases | No Cases |
| Unknown | 0.31 (0.14–0.67) | $p = 0.0029$ | 0.44 (0.12–1.61) | $p = 0.2139$ |

Results from regression models looking at glycemic control within the diabetic population, as a variable for acute uveitis and scleritis or episcleritis. Models are adjusted for age, gender, ethnicity, body mass index (BMI), the presence of connective tissue disorders, the degree of retinopathy, the presence of maculopathy and deprivation quintile.

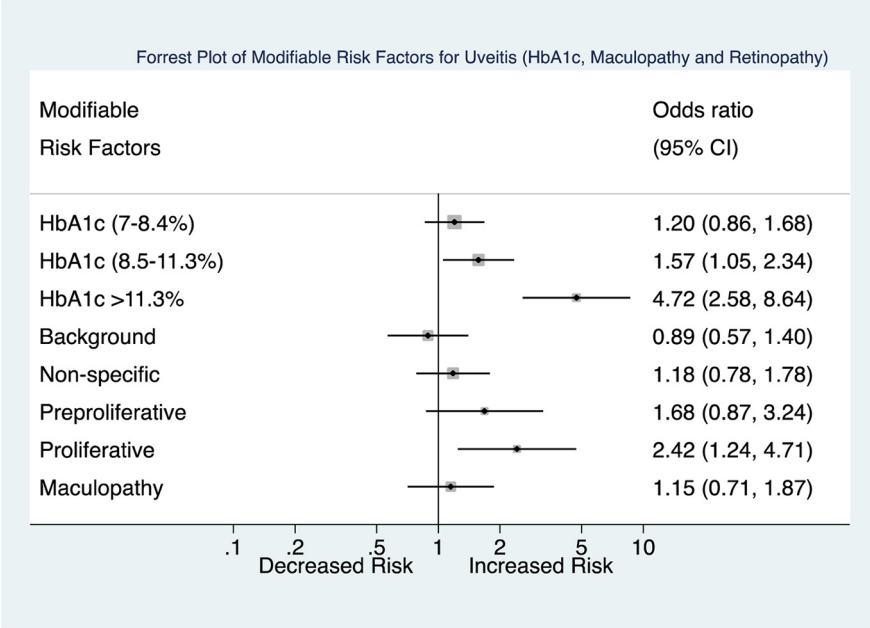


**Fig. 1.** Forrest plot of modifiable risk factors for uveitis (HbA1c, maculopathy and retinopathy). Caption: This visual representation of data reflects findings from the multi-variable logistic regression analysis constructed to establish risk factors for uveitis among diabetic populations (Table 3). This graph includes the odds ratios and corresponding 95% confidence intervals presented on a logarithmic scale.

Please cite this article as: Ansari AS, et al. Glycemic control is an important modifiable risk factor for uveitis in patients with diabetes: A retrospective cohort study establ.... (2018), https://doi.org/10.1016/j.jdiacomp.2018.03.008

likely due to the prism of secondary care referrals with our data being collected from a primary care source; this may indeed suggest many simple cases of episcleritis being managed in the community.

Information on the source of the diagnosis –whether this was made by GP or specialist—was not available in our dataset. It is therefore possible that there are cases where an incorrect diagnosis has been made. However current UK guidelines recommend that all suspected cases of uveitis, scleritis, and episcleritis are referred urgently to secondary care for management[27] and therefore the majority of diagnoses are likely to have been made by an ophthalmologist and coded retrospectively into the primary care record.

When considering the detection of concomitant eye disease, we acknowledge the possibility of ascertainment bias in the diabetic population. Diabetic Retinopathy guidelines published by the Royal College of Ophthalmologists suggest regular review for patients with signs of diabetic retinopathy. These vary between a few weeks to months before reassessment. Although this cohort of patients are indeed under close monitoring, uveitis is commonly an acute presentation that can be exceptionally painful and debilitating. Patients commonly seek urgent medical advice within a few days of onset and are immediately referred for ophthalmology review. While there may be a greater chance for ophthalmologists to detect conditions with insidious onset such as cataracts during routine screening, we would argue acute inflammatory presentations of uveitis or scleritis would not be discovered during routine ophthalmology assessments.

### 4.2. Comparison with the literature

There is a significant paucity of information that has been able to truly define the relationship between diabetes, uveitis or scleritis. Studies have been largely underpowered, have not attempted to define to a relationship or have simply attempted to look at ophthalmic outcomes in an attempt to better understand clinical course.

A recent systematic review highlighted this significant lack of information and conflicting reports relating to diabetes and intraocular inflammation. It highlighted the relationship between uveitis and diabetes and determined the need for more studies to conclude if an association truly exits.[12] This relationship between diabetes and anterior uveitis was first described >100 years ago.[28] With associations suggesting that patients with non-insulin diabetics to be more prone to suffer from idiopathic anterior uveitis in comparison to acute disease secondary to underlying systemic disease.[29] A number of different case resorts have highlighted the link between uveitis and diabetes.[30–32] With a number of authors even defining diabetes related uveitis occurring in the presence of poorly controlled diabetes without any other underlying cause of disease.[33,34] Only one other study has attempted to look characteristics of patients with uveitis and diabetic eye disease and was published in 2013.[34] This was disadvantaged by their population size ($n = 36$: type 1 = 1, type 2 = 35). They were however able to demonstrate a raised mean Hba1c of 9.5% (80 mmol/mol) in acute phases of disease. They also suggested an increased risk of progression of retinopathy stage due to poor glycaemic control for patients with recurrent disease. This dataset was collected from secondary care data, and thus was also able to report on visual outcomes and better classify type of uveitis. Another study attempting to examine cases of anterior uveitis in patients with diabetes ($n = 28$) found that patients without diabetic retinopathy were more likely to develop anterior uveitis and this was seen more frequently in patients who were being treated with insulin and glybenclamide.[35] Authors concluded that progression of disease and diabetes was not related to the presence of anterior uveitis. Other studies have looked to identify optimal treatment protocols for patients that suffer from uveitis. A team part of the 'visual loss in uveitis' based at Moorfields hospital in England identified 96 patients with chronic uveitis and a diagnosis of diabetes.[36] They however did not examine the role of glycaemic control on relapse rate. Patients with uveitis and diabetes appeared to have a significant reduction in visual acuity when followed up over two years.[36]

Many have postulated a possible immunological link between diabetes and uveitis.[37] One must remember that inflammation does indeed play an important role in the pathophysiology of both diabetic retinopathy and acute uveitis.[33,38] The basis of which is attributed to dysfunction of the blood-ocular barrier. This includes the up regulation of pro-inflammatory factors such as interleukin-1 Beta, IL-6, IL-8, interferon induced protein 10 and tumour necrosis factor alpha in diabetic retinopathy and over 16 different vascular endothelial growth factor independent inflammatory cytokines which have been implicated in proliferative retinopathy.[12] The earlier mentioned systematic review looking at the relationship between diabetes and uveitis identified a total of 82 reported case report or series on patients to have both diabetes and uveitis. Only 30 patients had type of diabetes highlighted, of which 76.7% of patients were type 1 and 23.3% having type 2 diabetes. Results that appear to be consistent with our findings with a total prevalence deemed to be between 7 and 13% of an underlying diagnosis of diabetes on first presentation with acute uveitis. However, they felt that there were conflicting results with some reports relating this high incidence of diabetes attributed to an aging population. Nonetheless, we have attempted to better delineate this relationship.

Information accurately describing the relationship, and clinical course of diabetic patients with scleritis or episcleritis is limited. A very few case reports have suggested possible diabetes as an underlying cause of infectious scleritis.[39] Studies attempting to establish the characteristics of those with scleritis have noted up to 20% patients with an underlying diagnosis of diabetes.[40] Despite these suggested associations, there has been no published epidemiological study that has examined the potential correlations between diabetes and anterior uveitis, scleritis/episclertis, or attempted to determine the role of glycaemic control in people with diabetes. This is despite suggestions that those with underlying diabetes have more severe forms of disease, leading to potentially catastrophic ocular and systemic outcomes.[41]

## 5. Conclusions

Poor glycaemic control further in diabetes increases the risk of acute uveitis, with patients that have an HbA1c over >11.3% (100 mmol/mol) almost 5 times more likely to have an event. Acute uveitis was also more common in those with proliferative retinopathy. Scleritis or episcleritis was not found to be associated with diabetes, glycaemic control, or retinopathy. Acute uveitis is more common in patients with diabetes; those at highest risk are patients with type 1 disease.

## Author contributions

ASA, Sdel and AMcG were involved in the conception and design of the study. ASA, AMcG, and WH were involved in data collection. ASA and AMcG carried out the statistical analysis and data interpretation. ASA drafted the manuscript. ASA, AMcG, Sdel, WH, NM and ST provided critical review of the manuscript and contributed to the final write-up. AMcG was the principal 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,

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Servier, Takeda. ST has received speaker fees, conference attendance or an advisory board member for Alimera, Allergan and Bayer.

Study guarantor: Dr. Andrew McGovern MRCP.

## Acknowledgements

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

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Please cite this article as: Ansari AS, et al. Glycemic control is an important modifiable risk factor for uveitis in patients with diabetes: A retrospective cohort study establ.... (2018), https://doi.org/10.1016/j.jdiacomp.2018.03.008