Glycemic Control and Risk of Infections Among People With Type 1 or Type 2 Diabetes in a Large Primary Care Cohort Study

Julia A. Critchley, Iain M. Carey, Tess Harris, Stephen DeWilde, Fay J. Hosking, and Derek G. Cook

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OBJECTIVE

Diabetes mellitus (DM) increases the risk of infections, but the effect of better control has not been thoroughly investigated.

RESEARCH DESIGN AND METHODS

With the use of English primary care data, average glycated hemoglobin (HbA_{1c}) during 2008–2009 was estimated for 85,312 patients with DM ages 40–89 years. Infection rates during 2010–2015 compiled from primary care, linked hospital, and mortality records were estimated across 18 infection categories and further summarized as any requiring a prescription or hospitalization or as cause of death. Poisson regression was used to estimate adjusted incidence rate ratios (IRRs) by HbA_{1c} categories across all DM, and type 1 and type 2 DM separately. IRRs also were compared with 153,341 age-sex-practice–matched controls without DM. Attributable fractions (AF%) among patients with DM were estimated for an optimal control scenario (HbA_{1c} 6–7% [42–53 mmol/mol]).

RESULTS

Long-term infection risk rose with increasing HbA_{1c} for most outcomes. Compared with patients without DM, those with DM and optimal control (HbA_{1c} 6–7% [42–53 mmol/mol], IRR 1.41 [95% CI 1.36–1.47]) and poor control (≥11% [97 mmol/mol], 4.70 [4.24–5.21]) had elevated hospitalization risks for infection. In patients with type 1 DM and poor control, this risk was even greater (IRR 8.47 [5.86–12.24]). Comparisons within patients with DM confirmed the risk of hospitalization with poor control (2.70 [2.43–3.00]) after adjustment for duration and other confounders. AF% of poor control were high for serious infections, particularly bone and joint (46%), endocarditis (26%), tuberculosis (24%), sepsis (21%), infection-related hospitalization (17%), and mortality (16%).

CONCLUSIONS

Poor glycemic control is powerfully associated with serious infections and should be a high priority.

Infections are widely considered to be a source of significant health care costs and to reduce quality of life among people with diabetes mellitus (DM) (1). Nevertheless, relatively few, large, well-designed, epidemiological studies have explored relationships between poorer control of DM and infections; previous studies have important limitations (1). Most randomized controlled trials (RCTs) of DM control have not

Population Health Research Institute, St George's, University of London, London, U.K.

Corresponding author: Julia A. Critchley, jcritchl@sgul.ac.uk.

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investigated the effect of improved glycemic control on infections and are unlikely to do so at present because of the high cost and lack of good-quality supporting observational evidence. One early landmark RCT, the Diabetes Control and Complications Trial, reported infection outcomes in a very restricted population (1,441 people with type 1 DM [T1DM] ages 13–39 years) (2) and showed substantial reductions in the risk of vaginal infections in the tight control group compared with the control arm (2). The benefit from tighter control also was seen after trial end in the observational follow-up (1,3). However, data on other infections in older people with type 2 DM (T2DM), in whom infections are more burdensome and risks of tighter glycemic control higher, are urgently needed. A recent review of higher-quality population-based epidemiological studies found clinically important (~1.5–3.5 times higher) infection risks associated with poorer DM control in some studies (usually defined as a glycated hemoglobin [HbA_{1c}] level >7–8% [53–64 mmol/mol]) (1). However, the studies were inconsistent, generating uncertainty about the evidence.

A key concern with previous work is that the measurement of HbA_{1c} usually was made at or near to the time of the infection, so any association could be explained by reverse causality. Any infectious disease episode can itself have an adverse effect on glycemic control, a process known as stress hyperglycemia (4); hence, blood glucose or HbA_{1c} measurements near the time of an infection may be elevated, rendering determination of the chronology and relationship between the two difficult. Several studies with serial HbA_{1c} measurements have shown that the stress hyperglycemia response can be substantial (4–6). Another important issue is that studies of incident DM often use measurements of HbA_{1c} obtained during initial presentation, and these typically do not represent subsequent levels after initiation of treatment; use of such measurements may obscure associations between usual HbA_{1c} level and infection risk. Other limitations of previous work include a lack of consideration of type of DM (especially T1DM) and fewer older people with DM. The current study uses a large English primary care database with repeated HbA_{1c} measurements wherein we can classify individuals more precisely in terms of their baseline glycemic control as well as ensure that these HbA_{1c} measurements were made before the infection episode.

RESEARCH DESIGN AND METHODS

Data Source

The Clinical Practice Research Datalink (CPRD) is a large primary care database representative of the U.K. population (7). The study is based on 361 general practices in England only, with anonymous linkage to Hospital Episodes Statistics and Office for National Statistics death registration data (8).

Study Design

We carried out a further analysis of a retrospective matched cohort study that we have previously reported on (8) (Supplementary Fig. 1). Initially, we identified all patients with DM (n = 104,717) as of 1 January 2008 who were alive and actively registered for at least 1 year, who were aged 40–89 years, and who had a Read code for DM (nationally agreed-on codes that practices are encouraged to use) (9). Two age-sex-practice–matched controls were selected from the remaining pool of similarly registered patients with no DM diagnosis by 1 January 2008. Patients with DM (n = 100) not matched with controls were excluded. Patient DM was classified as T1DM, T2DM, or type uncertain by using a combination of DM Read codes and prescriptions of anti-DM medications (insulin, sulphonylureas, biguanides, other) to estimate type as of 1 January 2008 (8) (Supplementary Fig. 2).

Ascertainment of HbA_{1c} Level

From the original cohort, we collated all recorded HbA_{1c} measurements on the 104,617 patients with DM between 1 January 2008 and 31 December 2009 (Supplementary Fig. 1) and calculated the mean HbA_{1c} for each patient. From these we excluded patients no longer active in CPRD on 1 January 2010 (n = 15,416): 6,636 had died during 2008–2009, 5,638 had transferred out of their practice, and 3,412 were from a practice that stopped contributing data to CPRD. Among active patients, 2,932 had no HbA_{1c} measured during 2008–2009, and 1,496 had no remaining controls by 1 January 2010. A small number of patients (n = 267) who had been classified as having T1DM were not prescribed insulin during 2008–2009 and were reclassified as type uncertain, resulting in 85,312 patients with DM (78,964 with T2DM, 4,496 with T1DM, 1,852 with type uncertain) and 153,341 matched controls who were eligible on 1 January 2010 for analysis of subsequent infection. All patients were followed until the earliest date of death, deregistration from practice, their practice leaving CPRD, or 31 December 2015. Mean follow-up time for all patients was ~4.2 years. To minimize the potential for infections influencing HbA_{1c} level among the 307,652 total HbA_{1c} measurements, we excluded any measurements (n = 5,029 [1.6%]) made within ±14 days of a recorded infection event occurring within the baseline HbA_{1c} assessment period (2008–2009).

Classification of Infections

Infections subsequent to the 2-year HbA_{1c} assessment period, recorded between 2010 and 2015, were classified into 18 different groupings by using Read codes for general practice data and ICD-10 classifications for hospital admissions and cause of death (Supplementary Table 1). For each group, all recordings within 90 days were assumed to be the same event, with codes >90 days apart assumed to be distinct events. The total number of infection events was counted for each patient. Three summary groups were defined: *1*) any infection with a prescription for an antibiotic, antifungal, or antiviral drug (British National Formulary section 5.1) (10) within 14 days of the diagnosis; *2*) any infection event that resulted in a hospital admission; and *3*) any infection that resulted in death.

Statistical Analyses

Poisson regression was used to estimate and compare incidence rate ratios (IRRs) of infection (Stata 13 statistical software), with an offset accounting for total days registered. We first carried out comparisons using patients without DM as the reference group. We fitted a model conditioned on the match sets to estimate differences in rates of infections between patients with and without DM. This model implicitly adjusts for age, sex, and practice. We also adjusted for smoking, BMI, and Index of Multiple Deprivation, a composite small-area ecological measure of deprivation based on postal codes (11). Additional adjustment for comorbidities (chronic kidney disease, heart failure, hypertension, hypothyroidism, ischemic heart disease, peripheral vascular disease, stroke and transient ischemic attack, and chronic

obstructive pulmonary disease) also was performed. In (nonconditional) Poisson models, we then fitted categories of mean HbA_{1c} (<6%; [42 mmol/mol], ≥6 to <7% [42–53 mmol/mol], ≥7 to <8% [53–64 mmol/mol], ≥8 to <9% [64–75 mmol/mol], ≥9 to <10% [75–86 mmol/mol], ≥10 to <11% [86–97 mmol/mol], ≥11% [97 mmol/mol]) with patients without DM first as the comparison group, now adjusting for age and sex. We stratified these models by age (40–64, 65–89 years) to describe effect modification by age. Finally, we refitted these models only on patients with DM by using HbA_{1c} between ≥6 and <7% (42 and 53 mmol/mol) as the reference category. To account for clustering by practice, all models used a sandwich estimator to obtain robust SEs.

Sensitivity analyses were performed using alternate summaries of glycemic control, which included fitting HbA_{1c} as a continuous variable, using the median value, and incorporating a time-dependent element to the value to account for measurements taken during follow-up (a repeated-measures analysis using mean HbA_{1c} calculated every 1 January for each individual if still active on the basis of measurements from the previous 2-year period). We also extended the exclusion period for HbA_{1c} measurements around any infection from 14 up to 30 or 90 days. None of these approaches changed the findings in a meaningful way, so we retained the baseline summary for the main results.

Within patients with DM, we calculated attributable risk fractions (AF%) (12) for all infections by estimating the percentage of infections that would not have occurred if all individuals had the same infection risk as those in the optimal control group of HbA_{1c} 6–7% (42–53 mmol/mol). The CIs were obtained by taking the 2.5th and 97.5th percentiles from 1,000 bootstrap simulations.

RESULTS

Supplementary Table 2 summarizes the distribution of mean HbA_{1c} during 2008–2009 for all patients with DM by age, sex, duration of DM, BMI, smoking, and deprivation. The distribution of mean HbA_{1c} during 2008–2009 also is shown in Supplementary Fig. 3 by DM type. Mean (SD) HbA_{1c} was ~1% higher for patients with T1DM (8.3% [1.4]) versus T2DM (7.4% [1.4]), with patients with T1DM more than twice as likely to have a mean HbA_{1c} ≥9% (26.9 vs. 11.0%). Patients whose DM was classified as type uncertain had mean HbA_{1c} levels similar to patients with T1DM (8.3% [1.6]). The mean number of HbA_{1c} measurements recorded during 2008–2009 was similar in both types (3.5 for T1DM, 3.6 for T2DM). Patients with T2DM were on average ~10 years older than those with T1DM (66.9 vs. 56.1 years in 2008) and far more likely to have been diagnosed in the past 5 years (47.2 vs. 7.3%). Poorer glycemic control (increasing categories of HbA_{1c}) were associated with younger age, longer duration of DM, deprivation, and obesity (Supplementary Table 2). Low HbA_{1c} (<6%) was unusual (1.7% of patients with DM), but more common in older age and strongly associated with BMI; one in five underweight patients (20.5%; BMI <20 kg/m^2) had a mean level <6%.

Glycemic Control and Infection Risk Among Patients With DM Compared With Controls Without DM

Crude infection rates during 2010–2015 estimated across 18 different categories confirmed consistently higher rates among patients with DM (Supplementary Fig. 4). For many infections (e.g., skin, cellulitis, candidiasis, bone and joint), crude rates tended to rise with increasing HbA_{1c}. Some infections (e.g., mycosis [other fungal], sepsis) also showed elevated rates among patients with DM in the lowest HbA_{1c} category (<6%).

Table 1 summarizes infection risk (any plus prescription, any hospitalization, and death as a result of infection) between patients with and without DM by first comparing the increase in risk associated with DM (DM vs. non-DM) and then comparing HbA_{1c} categories, with non-DM retained as the reference category. Associations between infection and DM were more marked for patients with T1DM (e.g., hospitalization IRR 3.34 [95% CI 2.82–3.96]) than for those with T2DM (1.70 [1.64–1.76]). Because of the small number of deaths among patients with T1DM, comparisons for death as a result of infection were estimated for all DM combined (2.44 [2.13–2.79]). Additional adjustment for comorbidity attenuated differences but did not explain the association between DM and infection (Supplementary Table 3).

Clear trends were observed for increasing risk of infection with poorer levels of glycemic control (Table 1). However, even patients with DM with good control were at an increased risk compared with matched controls without DM. Thus, compared with patients without DM, patients with DM and good control (mean HbA_{1c} 6–7%, IRR 1.41 [95% CI 1.36–1.47]) and those with poor control (≥11%, 4.70 [4.24–5.21]) had elevated hospitalization risks for infection. These risks were higher among patients with T1DM. For example, patients with T1DM with a mean HbA_{1c} ≥11%, had more than eight times the risk of hospitalization than their matched controls without DM (IRR 8.47 [5.86–12.24]), whereas for T2DM, this was four times higher (4.31 [3.88–4.80]).

The trend between increasing HbA_{1c} and infection risk was present in both younger (40–64 years) and older (65–89 years) patients with DM (Fig. 1). Associations were attenuated in the older groups but remained clinically important. Older patients with DM and mean HbA_{1c} ≥10% were still approximately five times more likely to die as a result of infection during follow-up than patients without DM and almost three times as likely to be hospitalized.

Glycemic Control and Infection Risk Within Patients With DM

When statistical models were fitted to patients with DM only, adjusting now for age and sex differences and mean HbA_{1c} (Table 2), the higher risks of infection with poorer glycemic control were confirmed. For example, patients with mean HbA_{1c} ≥11% were almost three times as likely to be hospitalized for infection (IRR 2.95 [95% CI 2.66–3.28]). Further adjustment for comorbidity did not substantially alter the risk estimates (Supplementary Table 3). Patients with T1DM still had higher rates of hospitalization (1.12 [1.01–1.24]) and death as a result of infection (1.42 [1.03–1.96]) than patients with T2DM, even after accounting for duration of DM. Despite the association between infection and duration of DM, mean HbA_{1c} remained a stronger predictor for all summary outcomes.

Adjusted associations between HbA_{1c} and infection for all patients with DM are detailed in Table 3 for the individual infection categories. The largest relative associations between the poorest level of glycemic control (HbA_{1c} ≥11%) and optimal control (6–7%) were seen for bone

Table 1—Adjusted IRRs for summary infection groups during 2010–2015 by mean HbA_{1c} level during 2008–2009, with patients without DM as the reference group

			Mean HbA_{1c} (2008–2009) in patients with vs. without DM[b]						
Outcome	Non-DM	DM vs. non-DM[a]	<6%	≥6 to <7%	≥7 to <8%	≥8 to <9%	≥9 to <10%	≥10 to <11%	≥11%
All DM (n = 85,312)									
Any plus prescription	1 (reference)	1.31 (1.30–1.33)	1.23 (1.18–1.29)	1.20 (1.18–1.22)	1.28 (1.25–1.30)	1.42 (1.39–1.46)	1.56 (1.50–1.62)	1.62 (1.53–1.72)	1.80 (1.70–1.90)
Any as hospitalization	1 (reference)	1.78 (1.72–1.84)	1.65 (1.54–1.76)	1.41 (1.36–1.47)	1.58 (1.52–1.65)	2.02 (1.91–2.13)	2.44 (2.26–2.64)	3.43 (3.14–3.75)	4.70 (4.24–5.21)
Death as a result of infection	1 (reference)	2.44 (2.13–2.79)	2.01 (1.71–2.37)	1.63 (1.45–1.85)	1.93 (1.70–2.19)	2.23 (1.86–2.66)	2.41 (1.85–3.14)	5.38 (3.98–7.26)	5.51 (3.83–7.93)
T1DM (n = 4,496) only									
Any plus prescription	1 (reference)	1.56 (1.47–1.65)	1.41 (1.08–1.85)	1.44 (1.26–1.64)	1.44 (1.32–1.56)	1.46 (1.34–1.59)	1.74 (1.56–1.93)	1.84 (1.59–2.13)	2.62 (2.17–3.16)
Any as hospitalization	1 (reference)	3.34 (2.82–3.96)	1.17 (0.52–2.63)	2.82 (2.17–3.67)	2.69 (2.17–3.34)	2.79 (2.25–3.45)	3.78 (2.96–4.83)	5.42 (3.96–7.42)	8.47 (5.86–12.24)
T2DM (n = 78,964) only									
Any plus prescription	1 (reference)	1.29 (1.28–1.31)	1.23 (1.17–1.28)	1.19 (1.17–1.22)	1.27 (1.24–1.29)	1.42 (1.38–1.46)	1.52 (1.46–1.58)	1.60 (1.50–1.70)	1.71 (1.61–1.81)
Any as hospitalization	1 (reference)	1.70 (1.64–1.76)	1.62 (1.52–1.73)	1.37 (1.32–1.43)	1.53 (1.46–1.59)	1.92 (1.82–2.03)	2.30 (2.11–2.50)	3.23 (2.93–3.55)	4.31 (3.88–4.80)

Data are IRR (95% CI). Number of (non-DM) age-sex-practice–matched controls: 153,341 all DM, 8,231 T1DM, 141,768 T2DM. Number of patients (%) with at least one infection event or died as a result of infection during follow-up: any infection plus prescription: 42,854 all DM (50%), 60,252 all non-DM (39%), 2,147 T1DM (48%), 2,828 non-T1DM (34%), 39,712 T2DM (50%), 56,243 non-T2DM (40%); hospitalization for infection: 11,320 all DM (13%), 10,333 all non-DM (7%), 551 T1DM (12%), 348 non-T1DM (4%), 10,769 T2DM (14%), 11,423 non-T2DM (8%); death as a result of infection: 1,106 all DM (1.3%), 1,058 all non-DM (0.7%). IRRs were adjusted for age, sex, smoking, BMI, and deprivation quintile. In the conditional model, age and sex were controlled through the matching. [a]Poisson model conditioned on match sets fits a term to compare DM with non-DM. [b]Poisson model now fits HbA_{1c} categories, with non-DM as reference category.

and joint infections (IRR 8.71), endocarditis (5.56), and sepsis (3.64). Five categories failed to show a clear trend with HbA_{1c}: eye infections, infective otitis externa, mycosis (other fungal), (acute) sinusitis, and (other) upper respiratory tract infection.

AF% for Infections in Patients With DM

Finally, we estimated AF% for the three summary groupings (Table 2) plus individual infection types (Table 3) across HbA_{1c} categories for patients with DM compared with the optimal control scenario of 6–7%. The largest AF% estimate was for bone and joint infections, with 46.0% of hospitalizations being attributed to HbA_{1c} values outside of the range 6–7%. Other large AF% estimates were observed for endocarditis (26.2%) and tuberculosis (23.7%), but CIs were wide. Sepsis (20.8%), pneumonia (15.3%), skin infections (cellulitis 14.0%, other 12.1%), and candidiasis (16.5%) all produced AF% estimates of ≥10%. Overall, 15.7% of infection-related deaths, 16.5% of infection-related hospitalizations, and 6.8% of infections requiring a prescription were attributed to values of HbA_{1c} outside the 6–7% range. These summary estimates were similar in a sensitivity analysis that used a time-updated HbA_{1c} measurement (Supplementary Table 4).

CONCLUSIONS

Across most categories of infection we considered, infection rates rose steadily with HbA_{1c}, which was particularly evident among those with the highest levels of HbA_{1c} (≥11%) and for T1DM. Among patients with DM, a more than doubling in the risk of hospitalization or death for infection was found; with the risk being higher in T1DM, the difference was only partially explained by the typically longer duration of DM among those with T1DM. In terms of the overall population effect, almost one-half of bone and joint infections among patients with DM were attributed to poor control. Diabetic foot complications are clinically well known to be strongly associated with infection risk (13), and almost one-half of infections in this broader category of bone and joint infections mentioned the foot as a focus of infection. The most novel and concerning finding is the substantial proportion of other serious infections statistically attributable to poor glycemic control, particularly

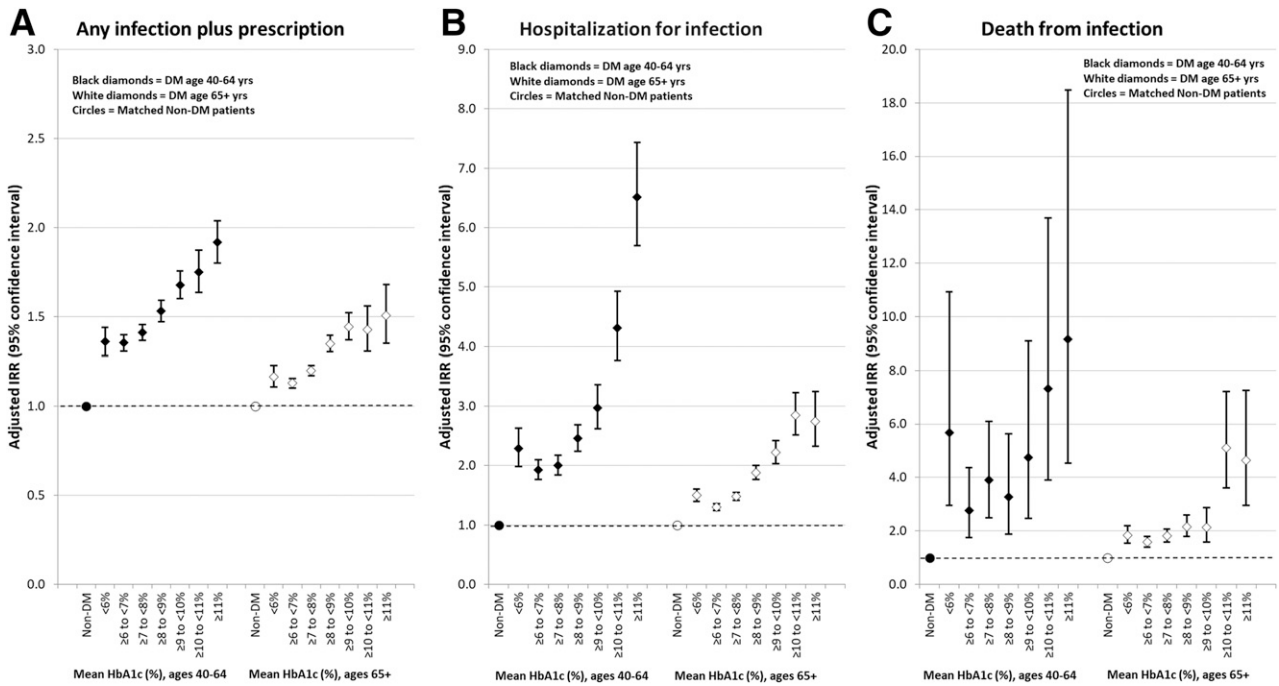

Figure 1—*A–C*: Adjusted IRRs for summary infection groups during 2010–2015 for all patients with and without DM by mean HbA_{1c} level during 2008–2009 (DM only) or non-DM status, stratified by age. Dotted line represents an IRR of 1.

endocarditis, tuberculosis, and sepsis. Between 20 and 30% of these infections in the English DM population could be attributed to poor control, although the 95% CIs were wide for tuberculosis and endocarditis because these infections are less common. Similarly, between 10 and 20% of other potentially significant infections, such as pneumonia, skin infections, sepsis, and candidiasis, as well as hospitalization and mortality as a result of infection were statistically attributed to poor glycemic control. Although some age attenuation was present, there were still clinically important increases in infection risks associated with poor control in the oldest age-groups where glycemic control can be more difficult and infection most common. Given the high risk of infection with increasing age (8), the absolute number of cases attributable to poor control will be higher at older ages.

Key Strengths

The key strengths of our analyses were the large data set, which contained many older patients (>36,000 age ≥70 years), and the comprehensiveness of the infection outcomes considered. By using primary care data linked to hospital episodes and mortality, we have been able to consider a whole range of common and rare, but serious infections not possible with previous epidemiological studies. Of note, our longitudinal design enabled us to first characterize the level of glycemic control (repeated HbA_{1c} measurements at baseline) well before the infectious disease episode, allowing us to be confident that the poor glycemic control preceded (and was not a result of) the infection episode. The large sample size also enabled us to consider the importance of several factors rarely considered in previous research, including key effect modifiers of the possible risk of infectious disease and more serious outcomes (e.g., age, socioeconomic status, BMI, type and duration of DM). Only DM duration had an appreciable effect on the magnitude of our estimates of risk. Therefore, we used the Bradford Hill criteria (14) to appraise the evidence for a causal relation between glycemia and infection risk. Overall, this appears high (Supplementary Table 5) given the temporality, strength, consistency, and dose-response relationship identified as well as the ability to adjust for key confounders in the current study.

Key Limitations

Although we designed this study to ensure that glycemic control was measured before the occurrence of infection, a key limitation is that these measurements became out of date over the lengthy follow-up (up to 6 years). Our approach differs from previous research in this field, which has usually been based on measurements of DM control at or near the time of infection, and hence, with less confidence about the temporality and direction of causation. To address this issue, we carried out a sensitivity analysis that incorporated a time-updated HbA_{1c} value during follow-up, but it did not make an appreciable difference in our estimates (Supplementary Table 4) possibly because *1*) mean within-patient HbA_{1c} was highly correlated during follow-up ($r > 0.7$ between consecutive 2-year periods) and *2*) the greater between-patient variation in HbA_{1c} was more influential in determining infection risk in the population cohort.

We did not have comprehensive data on the type of infection or organism identified because this is rarely available in primary care. The results were robust to adjustment for key confounders, but surveillance bias could be a possible explanation for some of the findings if a tendency exists to diagnose infections, prescribe antibiotics, admit to the hospital, and/or code death as infection related among patients with DM and higher HbA_{1c} levels. However, more

Table 2—Adjusted IRRs for summary infection groups during 2010–2015 by mean HbA_{1c} level during 2008–2009 among patients with DM only, with additional adjustment for duration of DM

Outcome	DM type[a]		Duration of diabetes (years)			Mean HbA_{1c} (2008–2009) in patients with DM (n = 85,312)					AF%[b]
	T2	T1	0–5	>5–15	>15	<6%	≥6 to <7%	≥7 to <8%	≥8 to <9%	≥9 to <10%	≥10 to <11%	≥11%	
Any plus prescription	1 (ref)	1.01 (0.97–1.06)	—	—	—	1.03 (0.98–1.07)	1 (ref)	1.05 (1.02–1.07)	1.15 (1.11–1.19)	1.24 (1.19–1.29)	1.27 (1.20–1.36)	1.40 (1.32–1.48)	6.8 (5.6–8.1)
	1 (ref)	0.90 (0.85–0.94)	1 (ref)	1.12 (1.10–1.15)	1.29 (1.25–1.33)	1.03 (0.99–1.08)	1 (ref)	1.02 (1.00–1.05)	1.10 (1.06–1.13)	1.18 (1.13–1.23)	1.21 (1.14–1.29)	1.32 (1.25–1.40)	
Any as hospitalization	1 (ref)	1.36 (1.24–1.50)	—	—	—	1.17 (1.09–1.25)	1 (ref)	1.09 (1.04–1.15)	1.34 (1.26–1.42)	1.58 (1.46–1.71)	2.18 (1.98–2.40)	2.95 (2.66–3.28)	16.5 (14.1–18.8)
	1 (ref)	1.12 (1.01–1.24)	1 (ref)	1.23 (1.17–1.28)	1.54 (1.44–1.64)	1.18 (1.11–1.27)	1 (ref)	1.05 (0.99–1.10)	1.23 (1.16–1.31)	1.43 (1.32–1.56)	1.98 (1.80–2.18)	2.70 (2.43–3.00)	
Death as a result of infection	1 (ref)	1.82 (1.33–2.48)	—	—	—	1.25 (1.05–1.49)	1 (ref)	1.14 (0.99–1.31)	1.24 (1.02–1.51)	1.31 (0.99–1.74)	2.90 (2.13–3.94)	3.01 (2.10–4.30)	15.7 (8.7–22.8)
	1 (ref)	1.42 (1.03–1.96)	1 (ref)	1.38 (1.20–1.59)	1.85 (1.53–2.25)	1.28 (1.07–1.52)	1 (ref)	1.06 (0.92–1.23)	1.10 (0.90–1.34)	1.13 (0.85–1.50)	2.51 (1.84–3.41)	2.65 (1.86–3.77)	

Data are IRR (95% CI) unless otherwise indicated. Ref category in Poisson models comprises patients with DM and HbA_{1c} between 6 and 7%. IRR adjusted for age, sex, smoking, BMI, deprivation quintile, and DM type. AR, attributable risk; ref, reference. [a]Type uncertain also fitted in model (estimates not shown). [b]AF% for infections for a baseline scenario of HbA_{1c} of 6–7% among all patients with DM. 95% CI calculated by taking the 2.5th and 97.5th percentiles from 1,000 bootstrap simulations.

serious infections diagnosed in the hospital would be supported by laboratory findings, and the associations with HbA_{1c} were strongest for such infections (8). Most of the covariates used are likely to be relatively stable over the period of the study, but medication use may vary; thus, reported associations on the basis of baseline usage may be attenuated. This study is based entirely on observational data, so we cannot consider the extent to which infection risk might be reversible if DM control improves.

Comparison With Previous Studies

The inclusion of hospital and mortality data as well as patients with T1DM may explain why we identified stronger associations than those identified in a similar U.K. primary care data set that estimated a 35% increase in infection risk for good versus poor glycemic control among only patients with T2DM (15). A study in Denmark found modest associations between HbA_{1c} levels >10.5% and infection risk among 69,318 patients with T2DM, which is up to 1.2 times higher for community infection and 1.6 times higher for hospital infections (16). Unlike the current study, the Danish study found stronger associations with more recent and time-updated measurements of HbA_{1c} than with earlier baseline measures. However, the Danish study included only incident T2DM, whereas ours was based on prevalent DM, which possibly explains the difference wherein newly diagnosed DM tends to have high levels of HbA_{1c} at the time of diagnosis that sometimes decline and become more stable with treatment. The Danish study also found that effects of poor glycemic control on infections were greater when microvascular complications were present (15) (although still significant when absent), whereas controlling for comorbidities made little difference in the current analyses (Supplementary Table 3).

Implications

Prevalence of diagnosed T2DM has tripled in the U.K. over the past 20 years (17). Although some improvements in glycemic control also have been observed over this period, our analyses show that substantial numbers of patients still have very poor glycemic control (e.g., 16% of patients with T2DM and 41% of patients with T1DM had a mean

Table 3—Adjusted IRRs and AF% for specific infections during 2010–2015 by mean HbA_{1c} level among patients with DM only

	Mean HbA_{1c} level (2008–2009) in patients with DM (n = 85,312)						
Category	<6%	≥6 to <7%	≥7 to <8%	≥8 to <9%	≥9 to <10%	≥10 to <11%	≥11%	AF%[a]
Bone and joint infections	1.12 (0.81–1.53)	1 (reference)	1.55 (1.26–1.91)	2.49 (1.95–3.17)	3.45 (2.62–4.55)	5.39 (3.95–7.34)	8.71 (6.64–11.41)	46.0 (37.5–54.0)
(Acute) Cholecystitis	1.03 (0.77–1.38)	1 (reference)	0.98 (0.81–1.20)	1.15 (0.90–1.47)	0.92 (0.64–1.32)	1.52 (1.05–2.19)	2.28 (1.53–3.39)	4.5 (−5.9 to 14.8)
Endocarditis	1.16 (0.43–3.12)	1 (reference)	1.38 (0.74–2.56)	1.17 (0.44–3.10)	1.72 (0.62–4.74)	5.01 (1.98–12.71)	5.56 (2.09–14.78)	26.2 (−5.3 to 56.3)
Eye infection	0.97 (0.87–1.08)	1 (reference)	0.95 (0.87–1.03)	1.01 (0.93–1.11)	1.13 (1.01–1.26)	1.02 (0.86–1.19)	1.16 (0.95–1.41)	−0.3 (−4.2 to 3.6)
Gastrointestinal infection	1.06 (0.92–1.21)	1 (reference)	1.05 (0.95–1.15)	1.16 (1.04–1.30)	1.23 (1.05–1.44)	1.51 (1.22–1.86)	1.84 (1.50–2.26)	8.0 (2.6–12.8)
Infective otitis externa	0.83 (0.69–1.01)	1 (reference)	0.99 (0.90–1.10)	1.06 (0.95–1.19)	1.05 (0.90–1.23)	1.01 (0.82–1.25)	0.98 (0.76–1.26)	−0.4 (−5.8 to 5.2)
LRTI	1.03 (0.97–1.10)	1 (reference)	1.06 (1.02–1.10)	1.16 (1.10–1.23)	1.26 (1.17–1.34)	1.27 (1.15–1.40)	1.25 (1.14–1.37)	6.7 (4.9–8.7)
Mycosis								
Candidiasis	0.93 (0.82–1.05)	1 (reference)	1.15 (1.07–1.25)	1.47 (1.35–1.59)	1.50 (1.36–1.67)	1.62 (1.41–1.86)	1.92 (1.66–2.22)	16.5 (12.5–20.1)
Other fungal	0.96 (0.86–1.06)	1 (reference)	1.04 (0.98–1.10)	1.05 (0.97–1.14)	0.95 (0.85–1.07)	0.93 (0.79–1.09)	0.88 (0.74–1.05)	0.7 (−3.1 to 4.6)
Pneumonia	1.23 (1.12–1.36)	1 (reference)	1.10 (1.03–1.17)	1.40 (1.28–1.52)	1.71 (1.51–1.94)	2.00 (1.69–2.38)	2.68 (2.26–3.17)	15.3 (11.9–18.5)
Sepsis	1.25 (1.06–1.47)	1 (reference)	1.20 (1.07–1.35)	1.53 (1.32–1.76)	1.69 (1.39–2.05)	2.36 (1.85–3.00)	3.64 (2.82–4.70)	20.8 (15.2–26.2)
(Acute) sinusitis	1.07 (0.93–1.23)	1 (reference)	1.06 (0.97–1.16)	1.14 (1.02–1.27)	0.98 (0.83–1.15)	0.91 (0.72–1.14)	0.86 (0.67–1.11)	3.5 (−2.1 to 9.6)
Skin								
Cellulitis	1.22 (1.13–1.32)	1 (reference)	1.07 (1.01–1.13)	1.28 (1.19–1.38)	1.63 (1.49–1.79)	1.74 (1.53–1.99)	2.29 (2.04–2.57)	14.0 (11.3–17.0)
Other	1.06 (0.98–1.14)	1 (reference)	1.06 (1.01–1.12)	1.23 (1.16–1.31)	1.45 (1.35–1.55)	1.52 (1.39–1.68)	2.04 (1.83–2.27)	12.1 (9.5–14.4)
Surgical site	0.98 (0.83–1.17)	1 (reference)	0.96 (0.84–1.09)	0.93 (0.79–1.10)	1.26 (1.04–1.53)	1.43 (1.10–1.85)	2.01 (1.56–2.60)	3.0 (−3.7 to 10.0)
Tuberculosis	0.27 (0.03–2.10)	1 (reference)	1.47 (0.75–2.87)	1.13 (0.50–2.53)	1.40 (0.55–3.59)	3.78 (1.39–10.26)	3.04 (1.21–7.64)	23.7 (−11.1 to 54.0)
(Other) URTI	0.95 (0.88–1.03)	1 (reference)	1.11 (1.06–1.16)	1.09 (1.03–1.16)	1.10 (1.02–1.19)	1.08 (0.97–1.20)	0.98 (0.88–1.10)	4.8 (2.2–7.5)
Urinary tract infection	1.01 (0.93–1.09)	1 (reference)	1.06 (1.00–1.11)	1.18 (1.10–1.27)	1.21 (1.10–1.34)	1.26 (1.11–1.42)	1.44 (1.24–1.67)	6.3 (3.6–8.6)

Data are IRR (95% CI) unless otherwise indicated. AR, attributable risk; LRTI, lower respiratory tract infection; URTI, upper respiratory tract infection. IRRs adjusted for age, sex, smoking, BMI, deprivation quintile. Reference category in Poisson models is patients with DM and HbA_{1c} between 6 and 7%. [a]AF% for infections for a baseline scenario of HbA_{1c} of 6–7% among all patients with DM. The 95% CI was calculated by taking the 2.5th and 97.5th percentiles from 1,000 bootstrap simulations.

HbA_{1c} >9%). The AF% of infections attributed to poor control of DM is already high and may even increase over time with rising DM prevalence and population aging. The U.K. has a relatively low prevalence of DM and good control on the basis of international comparisons (18); therefore, in many low- and middle-income countries, the burden of infections attributable to poor glycemic control could be substantially higher (19).

A variety of mechanisms may link DM and hyperglycemia with infection response (1,20–22). Diabetes progression itself is associated with immune dysfunction; autoimmunity in T1DM and low-grade chronic inflammation in T2DM (1). Hyperglycemia may also have adverse effects on several types of immune cells (19,23); alter cytokine and chemokine gene expression (24), and inhibit effects of complement (25). Other important mechanisms may include peripheral diabetic neuropathy because this results in a loss of sensation and reduced awareness of minor injuries (13). Alongside ischemia, often as a result of related peripheral arterial disease, neuropathy can result in impaired barrier defenses, skin ulcers, and lesions with poor wound healing and an increased risk of secondary infections (19). Although numerous mechanisms exist, nearly all involve poor glycemic control. Thus, that improved control would reduce infections seems likely (see Bradford Hill criteria in Supplementary Table 5). Achieving better glycemic control in practice is a complex issue, and the failure to do so has been related to clinical inertia in health care (26), particularly the failure to prescribe additional anti-DM medications when needed (i.e., insulin). Tackling this complex problem is the subject of ongoing research and may require a multifaceted approach (27), including wider membership of the health care team. Improved technology (e.g., to deliver insulin [27] and for patient self-monitoring of blood glucose) could help; less-invasive means of blood glucose testing (e.g., through saliva) also might assist with better control in the future (28).

Risk of infections and poor outcomes are likely to be worse in older patients. Although 14% of patients with DM in the current study were hospitalized for infection during follow-up, this figure rose to 22% among patients age 80–89 years (at baseline). RCT evidence has identified

limited benefits in terms of reducing mortality or macrovascular risk with tighter glycemic control among older people with DM of longer duration and at higher cardiovascular risk (29–32). However, these RCTs generally aimed for very tight control (HbA_{1c} <6 or <6.5%). Such levels may not be appropriate in frail older people with comorbidities who may be at higher risk of hypoglycemia and falls. The functional form of the relationship between HbA_{1c} levels and infection risk seem to be somewhat J shaped in this study, slightly higher for those with HbA_{1c} <6% for some infections (Supplementary Fig. 4), although after adjustment for confounders, this was statistically significant only for pneumonia, sepsis, and cellulitis (Table 3). An increased risk associated with very low HbA_{1c} has been seen in other studies of infections (16) as well as in some RCTs of cardiovascular and mortality outcomes that aimed for very tight control (29–32). This increased infection risk was associated with older age and low BMI in the current study so it may be identifying frail older people with limited life expectancy and a very high infection risk. More modest HbA_{1c} targets (~8% or just below) could potentially achieve substantial population benefit and reduce the risks associated with tighter control. Consideration of infection outcomes may potentially alter conclusions about the cost-effectiveness of better control among older people and hence, treatment targets and priorities (33).

Overall, the current analyses demonstrate a strong and likely causal association between hyperglycemia and infection risk for both T1DM and T2DM. DM duration and other markers of severity cannot explain the increased risk, nor can longer duration explain the increased risk for T1DM compared with T2DM. This remains the case in older people in whom infections are common and often severe and more uncertainty exists about the vascular benefits of improving DM control. Substantial proportions of serious infections can be attributed to poor control, even though DM is managed well in the U.K. by international standards. Interventions to reduce infection risk largely have been ignored by the DM community and should be a high priority for future research. Clinical trials should include patients with the poorest control, older age-groups, and patients with a history of significant infectious disease.

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