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Higher Incidence but Similar Outcomes from Bloodstream Infections in People with Type 2 Diabetes Mellitus: A Retrospective Case-Controlled Analysis

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ABSTRACT

Aims: People with type 2 diabetes mellitus are more susceptible to infections. This study aimed to compare the microbiology, incidence and clinical outcome of bloodstream infections (BSIs) in people with type 2 diabetes and matched controls amongst a cohort of hospital inpatients in the United Kingdom.
Methods: A retrospective analysis was conducted on all positive blood cultures obtained over a one-year period, identifying inpatients with type 2 diabetes and BSIs (n = 151). Matched controls were collated from the same cohort. Admission data were obtained from clinical coding. Patient outcomes were analysed in terms of 90-day mortality, length of stay (LOS) and admission rate to high or intensive dependency units (HDU/ICU). Microbial culture and clinical source of infection were compared between groups.
Results: Patients with type 2 diabetes comprised 10.6% of admissions but 21.1% (n = 151) of analysed BSIs (OR: 2.27, p < .001). Similar 90-day mortality rates were seen between people with type 2 diabetes (D) and controls (C) (D: 23/151, C: 28/151, p = .54). Mean LOS was also similar (D: 19.8 days, C: 21.1 days p = .62). In both groups, *Escherichia coli* was the most commonly isolated organism (D: 64/173, C: 55/171) and the urinary tract the most common identified primary site of BSI (D: 47/151, C: 45/151).
Conclusions: Whilst inpatients with type 2 diabetes have increased odds of experiencing BSIs, our single-centre study suggests a diagnosis of type 2 diabetes does not necessarily confer a worse outcome.

Introduction

People with diabetes mellitus have increased susceptibility to infections, including those of the lower respiratory tract, urine and soft tissues [1]. They are also at increased risk of developing bloodstream infections (BSIs) [2,3]. Mortality from infectious causes is higher in people with diabetes [4,5] but it has not clearly been demonstrated that this confers a poorer prognostic outcome in bacteraemia [2,6]. We sought to clarify the incidence, characteristics and outcomes of BSIs in adults with type 2 diabetes within our inpatient population at a large tertiary hospital in the United Kingdom.

Methods

We obtained retrospective data on all peripheral blood cultures yielding positive microbial growth from patients aged 18 years and over admitted to hospitals affiliated to Brighton and Sussex University Hospitals NHS Trust in the South East of England between 1st January and 31st December 2014 (n = 1973). The trust has just under 1000 beds and serves a population of around 540,000 people [7]. Single growths of probable contaminants including coagulase-negative *Staphylococci* (CONS), *Corynebacterium* spp., *Micrococcus* spp., *Peptoniphilus harei* and *Propionibacterium* spp. were excluded (n = 393).

The remaining cultures were collated into BSI episodes, defined by growth of one or more organism from an individual within a 31-day window; in patients with further positive blood cultures within 31 days, the first positive culture was included (n = 749). Patients with type 2 diabetes were identified within this group by review of patient records (n = 158). Seven people with type 2 diabetes were excluded from further analysis due to: insufficient clinical information (n = 3); mycobacterial growth (n = 1) or growth clinically considered

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contaminant (n = 3). Owing to the small size of the group, people with type 1 diabetes (n = 6) were excluded from analysis. The remainder were case-matched to a BSI control who did not have diabetes, by age, sex and date of BSI. Case-matched patient notes were reviewed for any evidence of diabetes including documented diabetes, diabetic medications, or raised glycosylated haemoglobin (HbA1c).

Clinical information including demographics, recent HbA1c (within 3 months pre- or post-BSI), and mortality data were elicited from electronic hospital reporting systems and clinical notes. Survival was assumed if mortality was not documented. Admission data were obtained from our clinical coding department. Statistical analysis was undertaken using Student's paired($^{\Delta}$) or Welch's two-sample($^{¥}$) t-test, or Fisher's exact test(†) on the Exact2x2 package, R version 3.2.3 (minimum likelihood method) [8] with a p value of <0.05 considered significant and 95% confidence intervals reported in the format [lower bound, upper bound].

Results

Of the 108,439 admissions in 2014, 1599 of these related to people with type 1 diabetes, and 11,518 to people with type 2 diabetes. Patients with type 2 diabetes therefore made up 10.6% of admissions and 21.1% (n = 151) of BSIs meeting inclusion criteria (OR: 2.27 [1.89, 2.71], p < .001). Given that local National Diabetes Inpatient Audit data reported a prevalence rate of 17.1%–18.3% of inpatients with diabetes [9], we performed additional analysis of coding data by diagnosis of type 2 diabetes and length of stay to check for under-reporting in the coding data. Using the same data that yielded an inpatient admission rate of 10.6%, we calculated an inpatient type 2 diabetes prevalence rate of 20.9%.

The mean age of BSI in people with type 2 diabetes (D) was 73.4 years (Range: 39–97 years) matched to 73.3 years in the control (C) arm (Range: 23–98 years). Groups comprised 58.9% and 59.6% men respectively. Seven cases and two controls experienced recurrent BSI with positive cultures more than 31 days apart. Each episode was therefore analysed individually.

Mean length of stay was similar between cases (19.8 days) and controls (21.1 days; p = 0.62$^{\Delta}$, 95% CI for difference of means [−4.0,6.7]). We observed no clear difference in 90-day mortality rates (D: 23/151, C: 28/151. OR: 0.79 [0.41, 1.46], p = .54†) or in rates of admission to High Dependency (HDU) or Intensive Care Units (ICU) in either group (D:33/151, C: 37/151, OR: 0.86 [0.50, 1.51], p = .68†) (Fig. 1).

A recent HbA1c was available for 67/151 patients with type 2 diabetes. Values ranged from 27 to 170 mmol/mol with a mean [±1 standard deviation] of 57.3 mmol/mol [35.2,79.3]. On subgroup analysis of those with a recorded HbA1c, there was no clear difference in mean HbA1c between 6/67 patients in the 90-day mortality group (51.7 mmol/mol) when compared to those who survived (57.8 mmol/mol) (p = .15$^{¥}$, 95% CI for difference of means [−14.6,2.4]). Additionally, there was no difference elicited in mean HbA1c between the eleven patients who required HDU/ICU admission (58.3 mmol/mol) and those managed at a ward-based level of care (57.1 mmol/mol) (p = .84$^{¥}$, 95% CI for difference of means [−12.0,14.5]).

Multi-growth BSI was observed in 17 cases and 14 controls. Therefore, groups cultured a total of 173 and 171 organisms respectively. The most commonly cultured organism was *Escherichia coli*, followed by non-*E. coli* coliforms in both groups (Table 1). *Streptococcus* species and *Staphylococcus aureus* were also prevalent. The urinary tract was the most common site determined as BSI source in both groups (D: 47/151, C: 45/151, OR: 1.06 [0.64, 1.76], p = .90†). Chest (D: 32/151, C: 27/151, OR: 1.23 [0.68,2.20], p = .56†), joint and soft tissue (D: 26/151, C: 24/151, OR: 1.10 [0.59, 2.10], p = .87†), and biliary tract (D: 19/151, C: 14/151, OR: 1.41 [0.66, 3.01], p = .46†) infections were also common. Intravenous catheter infections were uncommon but more prevalent in the control group (D: 5/151, C: 13/151, OR: 0.36 [0.12, 1.08], p = .08†).

Evaluation

Within our retrospective single-centre study, we observed BSI to be more than twice as common in admitted people with type 2 diabetes. As under-reporting of diabetes in clinical coding data could, artefactually, explain this result, we cross-checked, using prevalence data, that under-reporting is unlikely to be a major issue. We note a prevalence of inpatients with type 2 diabetes twice the admission rate, suggesting a mean length of stay of those coded with diabetes about twice than of those without. This is in keeping with the most recent available national audit findings [10].

When we compared people with type 2 diabetes to age- and sex-matched BSI controls, we found no significant differences in outcomes as measured by 90-day mortality, length of stay or HDU/ICU admission rates. These findings initially appear inconsistent with the paradigm that people with diabetes are more likely to die of infections [4]. Whilst our numbers of deaths at 90 days in BSI patients were too small to draw a meaningful statistical comparison, they are not inconsistent with current literature. Stoeckle *et al* found similar in-hospital mortality (18% *vs* 14%) in patients with BSI both with and without diabetes in Switzerland, [2] while Leibovici *et al* described rates of 28% and 29% in their 19-month prospective study [11].

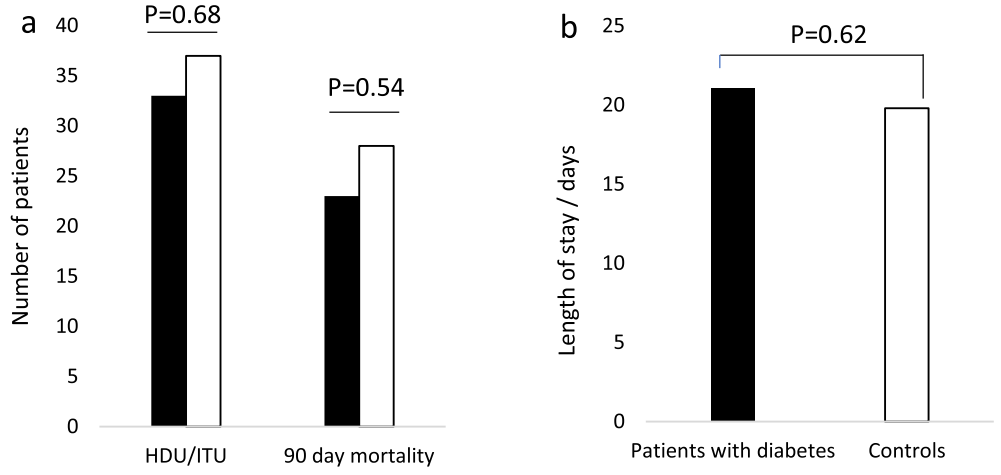

Fig. 1. Admission outcome of BSI in patients with type 2 diabetes compared to matched controls. a) Number of patients admitted to ITU/HDU and 90-day mortality [black – patients with type 2 diabetes; white – matched controls]. b) Comparison of mean length of stay.

Table 1
Microbiological isolates in patients with type 2 diabetes and matched controls.

	Patients with Diabetes (n = 173)	Controls (n = 171)	Univariate P Value†	Odds ratio	95% confidence interval
Bacillus	3	2	1.00	1.49	[0.22,12.13]
CONS	16	14	0.84	1.14	[0.54,2.51]
Enterococcus species	5	8	0.41	0.61	[0.19,1.95]
Escherichia coli	64	55	0.37	1.24	[0.78,1.95]
Haemophilus influenzae	0	2	0.25	0	[0,3.43]
Non-*E. coli* coliforms	23	17	0.57	0.79	[0.34,1.70
Proteus species	3	5	0.50	0.59	[0.12,2.44]
Pseudomonas species	10	13	0.53	0.75	[0.31,1.76]
Staphylococcus aureus	16	10	0.31	1.64	[0.70,3.82]
Streptococci - Alpha haemolytic	7	15	0.08	0.44	[0.16,1.09]
Streptococci - Beta haemolytic	12	12	1.00	0.99	[0.42,2.32]
Fungi	0	5	0.03	0	[0,0.99]
Others	14	13	N/A	N/A	N/A

Non-*E. coli* coliforms: Enterobacter cloacae, Bacteriodes fragilis, Citrobacter koseri, Hafnia alvei, Klebsiella pneumoniae, Klebsiella oxytoca, Enterococcus faecium and Serratia marcescens. CONS: Coagulase negative Staphylococcus - Included when 2 or more grown within timeframe and not clinically documented as a contaminant. Streptococci - Alpha haemolytic: includes S. pneumoniae.
† Fisher's exact test.

Our findings indicate reported increased mortality from infectious causes in people with type 2 diabetes and BSI is predominately due to a higher overall incidence and hence susceptibility to BSI, rather than poorer outcome when BSI is present. This is consistent with work by Bryan [12] and Carton *et al* [13] who postulated higher mortality from bacteraemia in people with diabetes driven by increased incidence, particularly from community-acquired urine infections. This suggests that a concentrated clinical approach to target reducing development of BSIs in people with diabetes could have a greater effect than aggressive management of prevailing BSIs. In practice, this would include earlier, thorough review and timely antibiotic treatment of common bacterial infections, as well as utilising prevention strategies such as patient education.

Hyperglycaemia during bacterial infection has previously been shown to correlate with mortality risk [14], consistent with *in vitro* data that a hyperglycaemic cellular environment produces dysregulation of immune cell functions [15,16]. It is unclear, however, whether this association results predominantly from poor long-term glycaemic control (as would be indicated by HbA1c) or a rise in blood glucose correlating with an acute physiological stress response. Our brief analysis of available HbA1c data did not demonstrate substantial correlation between HbA1c and the outcome of established infection. However, our sample size was small and the low proportion (67/151) of patients with recorded HbA1c level within three months of BSI means we cannot exclude an undetected underlying ascertainment bias relating to HbA1c levels.

We did not observe any clinically significant differences in the microbiology or source of BSI between groups. The urinary tract was the most commonly implicated source of BSI and *E. coli* the most cultured organism. Features of our control cohort, such as a higher predominance of indwelling catheter related BSIs and fungaemias, suggested increased predominance of co-morbidities, which could indicate additional risk factors such as complex infection or immunosuppressive chemotherapy. However, such a possibility would highlight the increased predominance of BSI in people with type 2 diabetes, even those without additional risk factors. The underlying difference in length of stay between those with diabetes mellitus and those without might result in an undetected difference between place of acquisition of infection, which may result in prognostic differences [17,18]; however, the similar lengths of stays between our cases and controls points away from this possible confounding.

Conclusion

This retrospective single-centre study demonstrated that hospital inpatients with type 2 diabetes have an increased risk of acquiring bloodstream infection; however, there was no clinically significant difference in outcome when compared to matched controls as measured by length of stay, requirement for HDU/ICU care and 90-day mortality. *E. coli* from urinary source continues to be a significant and prevalent cause of BSIs. BSIs remains an important complication in people with diabetes and awareness has the potential to reduce morbidity through early recognition, management and infection prevention.

Disclosures

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Declaration of competing interest

The authors have no conflicts of interest.

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