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ORIGINAL RESEARCH

Patterns and Impact of Hypoglycemia, Hyperglycemia, and Glucose Variability on Inpatients with Insulin-Treated Cystic Fibrosis-Related Diabetes

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ABSTRACT

Introduction: Mortality in patients with cystic fibrosis-related diabetes (CFRD) is higher than that in patients with cystic fibrosis without diabetes. Hypoglycemia, hyperglycemia, and glucose variability confer excess mortality and morbidity in the general inpatient population with diabetes.

Methods: We investigated patterns of hypoglycemia and the association of hypoglycemia, hyperglycemia, and glucose variability with mortality and readmission rate in inpatients with CFRD. All capillary blood glucose (CBG) readings (measured using the Abbott Precision web system) of patients with insulin-treated CFRD measured within our health board between January 2009 and January 2015 were. Frequency and timing of hypoglycemia (<4 mmol/L) and was recorded. The effect of dysglycemia on readmission and mortality was investigated with survival analysis.

Results: Sixty-six patients were included. A total of 22,711 CBG results were included in the initial analysis. Hypoglycemia was common with 1433 episodes (6.3%). Hypoglycemia ascertainment was highest between 2400 and 0600 h. Hypoglycemia was associated with a significantly higher rate of readmission or death over the 3.5-year follow-up period ($P = 0.03$). There was no significant association between hyperglycemia or glucose variability and the rate of readmission and mortality.

Conclusion: Among inpatients with CFRD hypoglycemia is common and is associated with an increased composite endpoint of readmission and death. As with previously reported trends in general inpatient population this group shows a peak incidence of hypoglycemic during the night.

Keywords: Cystic fibrosis-related diabetes; Glucose variability; Hyperglycemia; Hypoglycemia

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INTRODUCTION

Cystic fibrosis (CF) is a multi-organ disease caused by mutations in the CF transmembrane conductance regulator gene that which lead to ineffective clearance of secretions from epithelial surfaces [1]. The pancreas is one of the main organs affected. A large proportion of patients will require pancreatic enzyme replacement therapy for the damaged exocrine functions of their pancreas. According to the 2014 report of the UK Cystic Fibrosis Registry, 18.3% of UK patients with CF have a diagnosis of CF-related diabetes (CFRD) [2]. This percentage is likely to increase with increased longevity of patients with CF, as up to 47.5% of adult patients with CF have a significant glucose metabolism impairment [3].

The annual mortality rate among patients with CF in the UK is 1.5% [2], but in CF patients with a diagnosis of CFRD the mortality rate increases by threefold [4]. Insulin therapy has consequently been advocated to ameliorate the poor outcome associated with CFRD based on its proposed positive impact on the lung function of patients diagnosed with CFRD, as well as its ability to alleviate the rate of decline in pulmonary function tests (PFTs). Patients are occasionally started on insulin therapy in the absence of fasting hyperglycemia or at the impaired glucose tolerance stage when impaired first-phase insulin release causes high post-prandial glucose [5]. As well as impacting on PFTs, the reduction in postprandial glucose excursions with insulin therapy is thought to help increase body weight. This approach is not without risk as the use of insulin is associated with an increased rate of hypoglycemia [5].

Previous studies have shown that hypoglycemia, hyperglycemia, and glucose variability are additional risk factors for mortality and morbidity in the general inpatient population with diabetes [6–8]. We are not aware of any published study looking at the impact of these glucometric parameters on inpatients with a diagnosis of CF. The aim of this study was, therefore, to investigate patterns, frequency, and trends of hypoglycemia in the insulin-treated CF population of the National Health Service Greater Glasgow and Clyde (NHSGGC). We also investigated the association between hypoglycemia, hyperglycemia, and glucose variability, with morbidity (as measured by readmission rates) and mortality.

METHODS

All patients with CF whose healthcare needs were provided by the NHSGGC Health Board and their Community Health Index were identified. Individuals with inpatient capillary blood glucose (CBG) measurements that had been uploaded to the Precision Web Point-of-Care Data Management System (Abbott Diabetes Care Inc., Alameda, CA) during the time period January 2009 to January 2015 were identified and the data retrieved.

The analysis of CBG data involved linking these data to mortality datasets. Data on insulin use was obtained from the local departmental CF database. Dates of admission and discharge were identified from CBG data. The incidence and timing of biochemical hypoglycemia (defined as a recorded CBG value if <4 mmol/L) and hyperglycemia (defined as a recorded CBG value of >15 mmol/L) were identified during an index admission—defined as the first admission occurring during the study period. The interquartile range (IQR) of inpatient CBG values was calculated for each admission.

The association between the incidence of one or more episodes of hypoglycemia and a

composite endpoint of time to first readmission or death following the index admission (date of discharge to date of readmission or death) was investigated. The impact of incidence of hyperglycemia was similarly explored. Association of the IQR (top 50% vs. lower 50%) with first readmission or death was calculated. Additionally, the proportion of measured CBG values that were within the hypoglycemic range during a nocturnal time period (2400–0600 hours) versus daytime (0600–2400 hours) was calculated and compared to that of the daytime period (0600–2400 hours).

Statistical analysis of data was performed using R, a statistical computing environment [9]. Survival analysis was analyzed using the Cox proportional hazards model, including age at admission and duration of admission as covariables. The Chi-square test was used to compare the number of CBG measurements that were <4 mmol/L as a proportion of all CBG measurements performed during the daytime and nocturnal time periods.

This study was conducted in accordance with the Declaration of Helsinki. Informed consent was not required for this study.

RESULTS

A total of 291 patients with CF whose healthcare was provided by the NHSGGC Health Board were identified. Of all patients with CF, 126 had one or more CBG readings performed during the period of analysis. We identified a total of 1014 admission episodes and 22,711 CBG measurements for this group. Of these 126 patients, 66 were recorded as both receiving insulin therapy and having been admitted during the period of investigation. These latter 66 patients were included in the analysis and their characteristics are described in Table 1.

Hypoglycemia was common within the total CF inpatient population on insulin, with 1433 CBG values (6.3%) recorded within the hypoglycemic range across all admissions. The proportion of CBG measurements below the threshold for hypoglycemia in patients with CF on insulin therapy was higher during the nighttime (2400–0600; $P < 0.01$; Fig. 1).

Of the 66 patients included in the study, 64 (97%) were readmitted or died following the index admission during the follow-up period.

Table 1 Characteristics of insulin-treated patients with cystic fibrosis-related diabetes included in study

Characteristics	Value	Number of patients for whom data are available
Age (years)	29 [23.0–35.0]	66
BMI (kg/m^2)	20.7 [19.0–22.3]	51
Male	0.58 (38)	66
FEV1 (L)	50.0 [29.3–59.8]	46
FVC (L)	68.0 [55.5–81.0]	46
Readmitted post-index admission	0.95 (63)	66
Mortality during follow-up period	0.32 (21)	66

Values in table are presented as the median with the interquartile range (IQR) in square brackets or as the proportion with the number in parenthesis, as appropriate

IQR interquartile range, *BMI* Body mass index, *FEV1* forced expiratory volume in the first second, *FVC* forced vital capacity

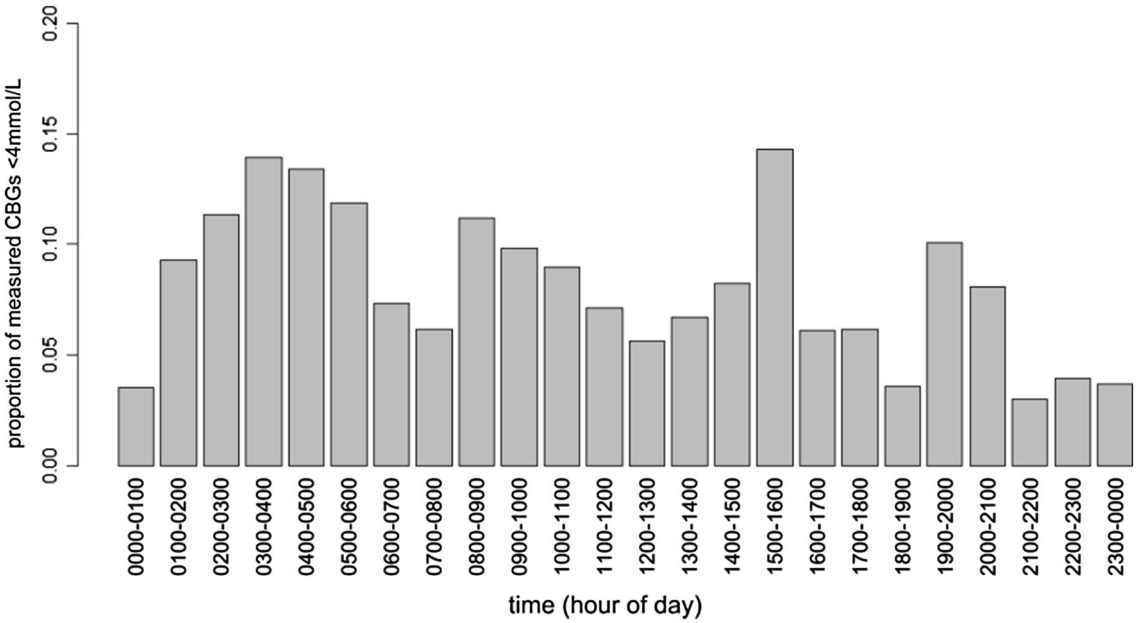

Fig. 1 Proportion of all capillary blood glucose (*CBG*) measurements that were within the hypoglycemic range (<4 mmol/L) by hour of day

Table 2 Characteristics of cystic fibrosis patients with and without recorded hypoglycemia

Characteristics	Hypoglycemia during admission		No hypoglycemia during admission		*P* value
	Value	Number of patients for whom data are available	Value	Number of patients for whom data are available	
Age (years)	29 [23–34]	33	28 [23–36]	33	0.7
BMI (kg/m^2)	20.2 [19.2–22.0]	24	21.3 [18.6–22.8]	27	0.3
Male	0.42	33	0.73	33	0.02*
FEV1	50 [30–59]	21	50 [29–60]	25	0.3
FVC	65 [55–71]	21	72 [57–82]	25	0.1
Number of CBG measurements per day	3.8 [2.7–5.5]	33	4.7 [3.0–12.2]	33	0.4

Values in table are presented as the median with the IQR in square brackets or as the proportion, as appropriate
CBG Capillary blood glucose

Thirty-three individuals had a hypoglycemic event during the index admission. Baseline and admission characteristics of those patients with and without hypoglycemia are shown in Table 2. There was no significant difference between the two groups when age, body mass index (BMI), forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), or median number of CBG tests performed per day were compared by the *t* test. There was a significantly greater proportion of males admitted who did not suffer a hypoglycemic

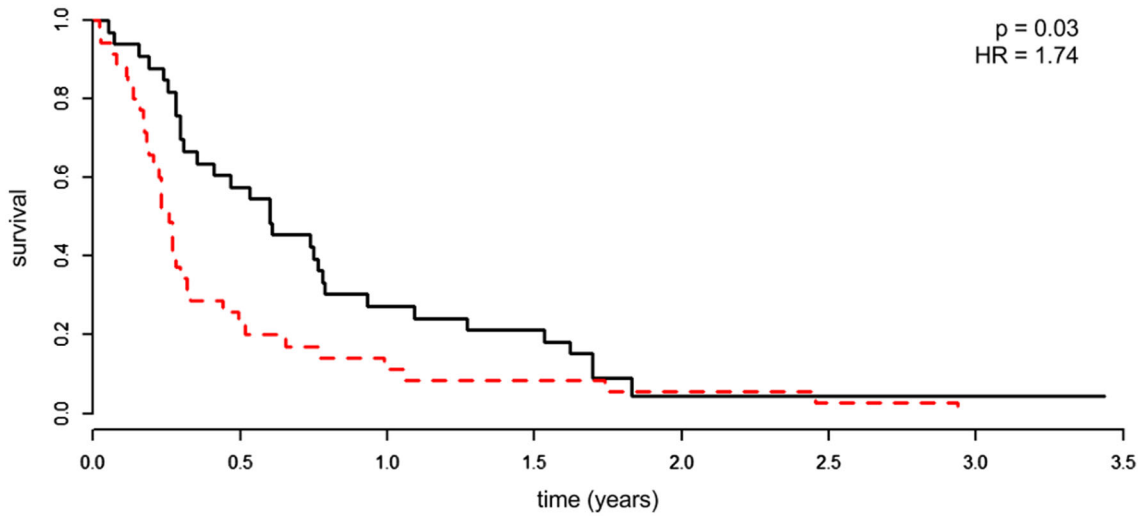

Fig. 2 Survival analysis to death or over a 3.5-year follow-up period. Group with recorded hypoglycemia during admission (*broken red line*) was compared to the group without hypoglycemia (*solid black line*). *HR* Hazard ratio

event. Of these, all (100%) were readmitted or died during the follow-up period, whereas 31 of 33 (94%) individuals without hypoglycemia were readmitted or died. Median time to readmission or death was 94 [95% confidence interval (CI) 69–161] days for those with hypoglycemia versus 219 (95% CI 129–340) days for those without. The occurrence of hypoglycemia was associated with a significant difference in time to first readmission or death on the survival analysis, with age and admission duration as covariables ($P = 0.03$; Fig. 2).

There was no significant association between hyperglycemia and time to first readmission or death, with a median time to the endpoint of 102 (95% CI 85–269) days in the hyperglycemia cohort and 149 (95% CI 108–282) days in the cohort without hyperglycemia ($P = 0.60$ on survival analysis). No difference in time to endpoint was observed in those individuals with high glucose variability (IQR values in the upper 50% of all IQR values when compared with those in the lower 50%; $P = 0.34$).

No significant excess mortality was identified in those with hypoglycemia (13/33, 39%) versus those without (8/33, 24%; $P = 0.47$ on survival analysis) and in those with hyperglycemia (10/21, 48%) versus those without (11/45, 24%; $P = 0.32$).

DISCUSSION

Identified biochemical hypoglycemia occurs more frequently in the inpatient population with insulin-treated CFRD than in the wider inpatient population with diabetes. In this study, 6.1% of the CBG measurements were in the hypoglycemic range, compared to 4.1% in a general diabetic population studied using the same methodology [9]. The higher rate of hypoglycemia seen in this group is likely to be due to the insulin therapy which all patients entered into our study were receiving. Local standard practice consists of a basal bolus regime with basal and prandial insulin analogs, as guided by the CBG measurements. Hypoglycemia may also be more common in the CFRD group secondary to diminished exocrine pancreatic function, with malabsorption, loss of glucagon response, and

reduced hypoglycemia awareness in patients with CFRD [10]. As with the general population with diabetes, hypoglycemia is more frequent during the nighttime [9]. This is potentially important as overnight CBG testing is often not part of routine diabetes management. It has previously been shown that a significant burden of nocturnal hypoglycemia is likely to be unrecorded secondary to the sporadic nature of overnight testing [9].

We have shown that hypoglycemia is associated with a significant increase in the rate of the composite endpoint of readmission and death over a 3.5-year follow-up period. With only one death occurring before the first readmission in this group, this finding is driven mainly by the increased rate of readmission. Hypoglycemia was associated with a non-significant increase in overall mortality. It is possible that episodes of hypoglycemia cause direct harm or predict a tendency for future deleterious hypoglycemic episodes causing adverse outcome. While no significant difference in available baseline characteristics or frequency of CBG testing were observed between those patients with and without hypoglycemia, it is likely that patients who are more ill and thereby readmitted more quickly have greater degrees of sepsis, liver disease, debility, and physiological derangement and are, therefore, more prone to hypoglycemia.

In our dataset, hyperglycemia and glucose variability did not show a significant association with readmission or mortality. In general, studies on diabetes inpatient populations have reported that hypoglycemia, hyperglycemia, and increased glucose variability are associated with excess morbidity and mortality [6–8]. It is likely that our dataset is underpowered to show any statistically significant increase in mortality associated with hypoglycemia, hyperglycemia, or glucose variability in this patient group.

Most of the hypoglycemic episodes were noted at the times when routine blood sugar monitoring was performed on the ward, which happens four times daily in our unit. This observation suggests that there may be a significant burden of hypoglycemia at other times of the day when CBG is not being tested. As hypoglycemia has been shown to confers excess mortality in the general inpatient population with diabetes, this possibility may be of clinical importance [6, 7].

This study had several limitations. Information gathering was difficult despite the introduction of electronic notes and the diabetes database (SCI-Diabetes). The dataset is quite small and heterogeneous, with patients having been started on insulin who have both impaired glucose tolerance and CFRD. We also lack data on other potential markers of poor outcome, such as sepsis, steroid use, enteral feeding, and transplantation. A larger, multi-center prospective study is required to determine whether the suspected trends of increased morbidity and mortality observed in this study are indeed significant. While individuals with CF are known to die earlier if they have diabetes, we do not have the data that would verify the benefit of tight glycemic control in CFRD or delineate fully the possible adverse outcomes [11].

CONCLUSIONS

Recommendations for Practice

A seven-point profile of blood sugar monitoring should be considered in inpatients with CF on insulin therapy, rather than the standard four-point profile. Patients with CF on insulin represent a high-risk group who experience fluctuations in their glycemic

control due to respiratory infections, concurrent steroid use, and physical stress. A seven-point profile will facilitate the identification of patients with hypoglycemia and postprandial hyperglycemia more readily. Doses of insulin can then be adjusted in a timely and accurate manner.

This study highlights the need for adequate resources dedicated to specialist diabetes input to inpatients with CFRD. Appropriate training and access to guidelines should also be in place for all medical staff and ward nurses who are in charge of the day-to-day prescription and administration of insulin to this group of vulnerable patients.

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Compliance with Ethics Guidelines. This study was conducted in accordance with the Declaration of Helsinki. Informed consent was not required for this study.

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