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Inpatient Glycemic Variability and Long-Term Mortality in Hospitalized Patients with Type 2 Diabetes

Joseph G. Timmons [a], Scott G. Cunningham [b], Christopher A.R. Sainsbury [a], Gregory C. Jones [a,*]

[a] Diabetes Centre, Gartnavel General Hospital, 1053 Great Western Road, Glasgow, G12 OYN, Scotland, United Kingdom
[b] Clinical Technology Centre, Ninewells Hospital, Dundee, DD2 1UB, Scotland, United Kingdom

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ABSTRACT

Aims/Hypothesis: To determine the association between inpatient glycemic variability and long-term mortality in patients with type 2 diabetes mellitus.
Methods: Capillary blood glucose (CBG) of inpatients from 8 hospitals was analysed. 28,353 admissions identified were matched for age, duration of diabetes and admission and median and interquartile range of CBG. 6 year mortality was investigated for (i) those with CBG IQR in the top half of all IQR measurements (matched for all except IQR), vs those in the lower half and (ii) those with the lowest quartile median glucose (matched for all except median).
Results:
1. Glycemic variability: 3165 matched pairs were analysed. Mortality was greater in those with IQR in upper 50% (≥50.9 mg/dl) over follow-up from day 90 post-discharge to a maximum of 6 years ($p<0.01$, HR 1.17).
2. Median glucose: 3755 matched pairs were analysed. Mortality was lower in those with a median glucose in upper 50% (≥148.5 mg/dl) over follow-up from day 90 post-discharge to a maximum of 6 years ($p<0.01$, HR 0.87).
Conclusion: Higher inpatient glycemic variability is associated with increased mortality on long-term follow up. When matched by IQR, we have demonstrated higher median CBG is associated with lower long-term mortality. CBG variability may increase cardiovascular morbidity by increasing exposure to hypoglycaemia or to variability per se. In hospitalized patients with diabetes, glycemic variability should be minimised and when greater CBG variability is unavoidable, a less stringent CBG target considered.

1. Introduction

Diabetes mellitus is an increasingly common and important condition worldwide, with an estimated growth to 366 million diagnoses by 2030 (Wild, Roglic, Green, Sicree, & King, 2004). With this increasing burden of disease worldwide, the importance of optimal management of diabetes will be a progressively greater challenge over the coming years. There is definitive evidence of deleterious effects of hyperglycaemia on long-term patient outcomes, with increased risks of both micro and macrovascular complications of diabetes (Duckworth et al., 2009; Patel et al., 2008; Stratton et al., 2000; UK Prospective Diabetes Study (UKPDS) Group, 1998). This association led to an emphasis on tight glycemic control. A major side effect of this approach however, is an increased prominence of hypoglycaemia (Action to Control Cardiovascular Risk in Diabetes Study Group, 2008). Hypoglycaemia triggers activation of counterregulatory hormonal systems and is associated with multiple negative effects, including cardiovascular events and death (Hanefeld, Duetting, & Bramlage, 2013; Johnston et al., 2011; Wei et al., 2000; Zoungas et al., 2010). More recently, there has been interest in whether fluctuations in glucose are important over and above low and high absolute levels, with increasing evidence to suggest that high glycemic variability is associated with negative outcomes (Frontoni et al., 2013).

Amongst hospitalized patients, patients with diabetes mellitus are over represented and may account for up to 25% of an inpatient population despite accounting for only 5–8% of the general population (Clement et al., 2004). While complications of glycemic control may lead to admission to hospital in these patients, admission is often for other medical or surgical conditions. Aside from the pathology leading to admission to hospital, the management of pre-existing diabetes must be an important consideration in optimal holistic patient management. It has previously been unequivocally demonstrated that length of hospital stay and mortality is increased in patients with diabetes (Brodovicz, Mehta, Zhang, et al., 2013; Clement et al., 2004; Nirantharakumar et al., 2012). This is perhaps due in part to suboptimal management of underlying diabetes. Intercurrent illness in itself, can also destabilise diabetic control making the achievement of optimal glycaemia even more challenging in the inpatient setting (Nirantharakumar et al., 2012).

The importance of hyperglycemia and hypoglycemia has been extensively explored within a hospital setting, but there has been less scrutiny of glycemic variability as an independent marker of poor

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* Corresponding author.
E-mail address: g.jones3@nhs.net (G.C. Jones).

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outcome (Frontoni et al., 2013). There is evidence that the variability of blood glucose has a bearing on the incidence of microvascular and macrovascular diabetic complications (Gimeno-Orna, Castro-Alonso, Boned-Juliani, & Lou-Arnal, 2003; Zoppini, Verlato, Targher, Bonora, et al., 2008). There has also been some evidence that suggests increased mortality associated with increased glycemic variability (Zoppini, Verlato, Targher, et al., 2008).

Despite the increased interest in glycemic variability in recent years, and the increasing evidence of its negative impact, there are few large-scale studies examining the effect of high glycemic variability on long-term outcome and mortality. Limited evidence is available of whether the negative effects identified *in vitro* translate into patient outcomes. Moreover, there is little evidence as to what glycemic target should be set in hospital inpatients, so as to mitigate any risk associated with high glycemic variability.

This study sought to test the hypothesis that high glycemic variability as a hospital inpatient, is independently associated with increased mortality on long-term follow up.

2. Methods

2.1. Data management

All inpatients who underwent capillary blood glucose (CBG) monitoring within the Greater Glasgow and Clyde NHS health board (NHS GGC) area between January 2009 and January 2015 were included in an initial acquisition of data. Data was drawn from the Abbott Precision Web glucose monitoring system used throughout NHS GGC. Quality control of this system has local oversight from the clinical laboratory service, with external oversight being provided by national reference laboratories.

This inpatient CBG dataset was merged with a national diabetes register (SCI Diabetes) – which contains information on all patients with a coded diagnosis of diabetes within Scotland – to obtain a data subset comprising all patients with diabetes mellitus in whom CBG values were monitored during the period of interest. Analysis was performed on those individuals with a recorded diagnosis of type 2 diabetes only. A single admission for each individual was analysed. The first chronological admission in the dataset where there were 4 or more recorded CBG values (to allow meaningful calculation of glucose excursion metrics) for each individual was analysed. Mortality data from SCI Diabetes (ultimately drawn from the national Information Services Division (NHS Scotland) mortality dataset) were linked to the CBG dataset. As far as can be ascertained, this dataset is complete (with the exception of individuals who may have left Scotland during the period of study).

Age was calculated from the unique patient identification (CHI) number, which contains within it the date of birth. Duration of diabetes was calculated from the date of admission and the date of diagnosis contained within the SCI Diabetes dataset. Duration of admission was calculated from the CBG data, taking the time of the first CBG measurement as the time of admission, and the time of the last contiguous CBG where the time between CBG measures is less than 5 days, as the time of discharge. Median and interquartile range (IQR) of inpatient CBG values were calculated for each admission. Biochemical episodes of hypoglycaemia were calculated for each admission, with an episode of hypoglycaemia defined as a contiguous series of CBG measures <72 mg/dl where the time interval between each measure was <60 minutes.

2.2. Case/control identification and matching

Cases were selected according to the analysis being performed. To investigate the association between glucose variability and survival, cases - those with a CBG IQR within the upper 50% of all IQR values - were matched with controls. Controls for each case were drawn from the set with IQR values within the lower 50% of all IQR values. Controls were additionally matched using the variables of age (+/− 5 years), duration of diabetes (+/− 5 years), duration of admission (+/− 0.5 days), median CBG during admission (+/− 2.25 mg/dl) and number of episodes of hypoglycaemia. Where the median CBG was the metric under test, cases were drawn from admissions with a median CBG within the upper 50% of median CBG values, with controls drawn from the lower 50%. As above, controls were matched using age, duration of diabetes, duration of admission and number of episodes of hypoglycaemia. In this analysis, matching included the CBG IQR (+/− 2.25 mg/dl). Where multiple matched controls were identified, a match was selected from the available pool of controls at random. A unique control was used for each case (controls were not reused). Survival over a maximum 6 year follow up period was examined using survival analysis and Cox proportional hazards model, with the parameter under investigation as a covariate.

2.3. Early mortality

The confounding effect of inpatient and early post-discharge mortality was considered to be potentially significant. Analyses investigating survival from the point of discharge, 30, 60 and 90 days post-discharge to the end of the follow-up period were examined. Analyses including time points earlier than 90 days post-discharge demonstrated a continuously changing gradient of the survival curve - thought to represent the effect of elevated mortality associated with the acute admission. Given the assumption of a constant relative hazard inherent within the Cox model, it was important to begin the survival analysis after this 'early' mortality effect had diminished, and 90 days post-discharge was therefore chosen as the start point for the survival analysis.

3. Results

Data associated with 28,353 unique individuals with diabetes mellitus, who had had one or more admissions were identified. 24,181 individuals had a coded diagnosis of type 2 diabetes mellitus.

Glucose variability analysis: 3165 matched pairs were identified. A table of comparative values for each of the matching parameters for case and control groups is shown in Table 1.

Higher inpatient glycemic variability was demonstrated to be associated with decreased survival from day 90 post-discharge over follow up for a 6 year period ($p < 0.01$) (Fig. 1). Hazard Ratio for mortality was 1.17 in the higher variability group. Table of demographics and matching parameters for case and control groups is shown in Table 1.

Median CBG analysis: 3755 matched pairs were identified. A table of comparative values for each of the matching parameters for case and control groups is shown in Table 2.

Higher inpatient median CBG was demonstrated to be associated with increased survival from day 90 post-discharge over follow up for a 6 year period ($p < 0.01$) (Fig. 2). Hazard Ratio for mortality was 0.87 in the higher variability group. Table of demographics and matching parameters for case and control groups is shown in Table 2.

Table 1
Legend: characteristics of case and control groups (IQR analysis). Values given as median (IQR).

	Case	Control	p
n	3165	3165	-
n male	1911	1866	0.3
IQR	3.8 (3.2–4.9)	1.9 (1.4–2.4)	<0.001
Age	69.8 (61.0–76.6)	69.7 (61.3–76.8)	0.80
n hypoglycemic episodes	386	386	-
Diabetes duration (years)	8.2 (4.5–12.1)	7.6 (4.2–11.6)	0.75
Admission duration (days)	3.2 (1.7–5.8)	3.2 (1.7–5.8)	0.81
Inpatient median glucose	8.7 (7.4–10.2)	8.7 (7.4–10.2)	0.97

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