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

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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 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 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.

Key words:

Diabetes

Glucose variability

Hypoglycaemia

Inpatient care

Introduction

Diabetes mellitus is an increasingly common and important condition worldwide, with an estimated growth to 366 million diagnoses by 2030. (1) 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. (2,3,4,5) This association led to an emphasis on tight glycemic control. A major side-effect of this approach however, is an increased prominence of hypoglycaemia. (6) Hypoglycaemia triggers activation of counterregulatory hormonal systems and is associated with multiple negative effects, including cardiovascular events and death. (7,8,9,10). 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. (11)

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. (12) 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. (12,13,14) 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. (13)

The importance of hyperglycemia and hypoglycemia have been extensively explored within a hospital setting, but there has been less scrutiny of glycemic variability as an independent marker of poor outcome. (11) There is evidence that the variability of blood glucose has a bearing on the incidence of microvascular and macrovascular diabetic complications. (15,16) There has also been some evidence which suggests increased mortality associated with increased glycemic variability. (17)

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.

Methods

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.

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 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.

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 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.

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 ($p<0.01$) (figure 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 ($p<0.01$) (figure 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.

Discussion

As the global burden of diabetes increases, the importance of achieving optimal glycemic management to reduce impact on resources, morbidity and mortality, becomes a greater priority. (1,12,13,14).

The concept of monitoring glycemic variability, and its importance in the optimal management of patients with diabetes has gained increasing attention. (11) The data from this study supports the use of measures of glycemic variability as a means of identifying inpatients at elevated risk of long-term increased mortality, and raises the potential of targeting glycemic variability with the aim of improving outcome.

Hyperglycaemia is accepted as contributing to increased incidence of the macro and microvascular complications of diabetes. In hospital inpatients, multiple epidemiological studies in a variety of inpatient settings have demonstrated increased mortality associated with hyperglycaemia. These findings led to studies aiming for tight glycemic control. (2,3,4,5)

Hypoglycaemia is a major complication of tight glycemic control. (6) The presence of hypoglycaemia has been demonstrated to contribute to worse outcomes in hospital

inpatients. (7,8) Hypoglycaemia in hospital inpatients is associated with increased mortality and length of stay. (9,10) This study demonstrated an association between a median CBG within the lower 50%, and increased mortality on long term follow up. This excess mortality may be a reflection of increased predisposition to hypoglycaemia.

The mechanisms through which hypoglycaemia is associated with mortality are complex. The adverse impact of hypoglycaemia on the cardiovascular system may be mediated by activation of the sympathetic nervous system and enhanced activation/aggregation of thrombocytes. Hypoglycemia has also been associated with repolarization abnormalities and increased inflammation which may partially explain adverse outcomes. Cardiovascular disease is the most common cause of death in patients with diabetes. It is therefore likely that hypoglycaemia acts as an additional risk factor which further adds to the risk to cardiovascular mortality. (7)

Our data support the hypothesis that there is increased mortality associated with high inpatient glycemic variability. This may be explained by negative molecular consequences of fluctuations in blood glucose. There is evidence both *in vivo* and *in vitro* that there are negative biological cellular effects associated with high glycemic variability. (18,19,20,21) Harmful oxidative free radicals have been demonstrated to be present in high glycemic variability and may contribute to these effects. Intermittent glycemic spikes have been shown to enhance apoptosis in cultured human cells, more so than consistently high glucose exposure, possibly due to overproduction of superoxides in mitochondria. (18,21,22) Several human studies have also demonstrated deleterious oxidation products associated with glycemic variability. Intermittent high glucose exposure has been shown to be associated with both increased levels of oxidative stress markers, and endothelial dysfunction in

patients with type 2 diabetes. (18,21) In elderly patients with type 2 diabetes, an independent association has been shown between increased coefficient of variation of fasting plasma glucose, and both all-cause and cardiovascular mortality. In agreement with our own data, survival analysis of this study demonstrated that glucose variability was detrimental in its own right, regardless of whether overall glycemic control was good or poor, as indicated by a high or low mean fasting plasma glucose level. (17) A substudy of the Veterans Affairs Diabetes Trial (VADT) has demonstrated a link between severe hypoglycaemia and progression of atherosclerosis. Although severe hypoglycaemia was seen more commonly in intensive glycaemia control patients, severe hypoglycaemia was only associated with atherosclerosis progression in the standard therapy arm of the study. This may be explained by increased glycemic variability, in that participants in the standard control group may have had greater glycemic excursions to reach glucose levels associated with severe hypoglycaemia. (23)

Our data demonstrate that long-term mortality is elevated in patients with increased glycemic variability. This increased mortality continues on an ongoing basis during follow up. It is possible that inpatient variability is a marker for ongoing post discharge variability, which may be harmful in itself, or increase potential for significant hypoglycaemia. On matching for median blood glucose level, it appears that glycemic variability is an independent marker for poorer outcome. However, patients with a lower median blood glucose level had a higher mortality than those with a higher median blood glucose level, when matched for glycemic variability. This may reflect a susceptibility for those with a lower median blood glucose to superimposed hypoglycemic excursions and potentially additional associated negative effects associated. In this scenario, the possibility of a higher risk of cardiovascular

mortality may be associated with the cumulative effect of both increased exposure to hypoglycaemia, and the negative vascular consequences of high glycemic variability. It has recently been demonstrated that in insulin treated diabetes patients, a peri-operative glucose target of <180 mg/dl may be harmful, whereas in non-insulin treated patients, a lower target may confer benefit. (24) It is possible that the higher glucose variability seen in insulin treated patients contributes to this observed difference. Our data raises questions around the traditional view of targeting tight blood glucose control in hospital inpatients. Indeed, our data would suggest that patients who achieve a higher median inpatient blood glucose could do better in the long-term.

Our data support the potential role of of glycemic variability in determining risk of long-term mortality in diabetic inpatients. Reducing glycemic variability is an attractive potential approach to attempt to reduce the high mortality in this group. In patients in hospital with high glycemic variability, consideration should be given to the treatment approaches used with the aim of reducing both inpatient variability, and any potentially adverse glycemic profile post discharge. Certain therapeutic options may help to reduce glycemic variability. (25) GLP-1 analogues, DPP-4 inhibitors, CSII and the new ultraslow insulin analogue degludec, have been shown to reduce glycemic variability, and this may confer benefit. (26,27,28). Further study in this area would provide more guidance, and would allow clinicians to change patient regimens with a view to reducing their glycemic variability. In some clinical settings, where high glucose variability exists, aiming for a higher inpatient glycemic target range may reduce the risk of harm, by limiting the opportunity for glycemic excursions into the hypoglycemic range.

Our study is limited by its retrospective design, and by the absence of other markers of illness severity for which we could match within our available data set. It is unclear whether inpatient glucose variability reflects later, post discharge, variability in glucose - or is simply a surrogate marker for the physiological derangement of severe illness. This is an area where further research into the extent to which inpatient glycemic variability translates into day to day variability after discharge would be useful.

Conclusion

Our data suggest that high inpatient glycemic variability is independently associated with excess mortality, in patients with type 2 diabetes mellitus on long-term outpatient follow-up. This may be as a result of the known deleterious effect of elevated glycemic variability on the vasculature. For any given level of glycemic variability, patients with lower inpatient median glucose levels had increased mortality when compared with those with higher median glucose levels. Inpatient glycemic targets could aim to reduce glycemic variability, and high inpatient variability may be a useful indicator of a high risk of adverse post-discharge glucose profiles. In patients with difficult to control high glycemic variability, aiming for higher average inpatient blood glucose levels may be appropriate to attempt to improve outpatient survival.

Further research is required to identify whether inpatient variability predicts adverse glucose patterns post discharge, and whether an approach that reduces glucose variability can reduce morbidity or mortality.

Acknowledgements

None

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Figure 1

Legend: 6 year survival analysis of individuals with IQR in upper 50% (>=50.9 mg/dl) (red) vs those with IQR in lower 50% (black). 3165 matched pairs, matched for age, duration of diabetes, duration of admission, inpatient median glucose and number of episodes of hypoglycaemia. HR for mortality (upper vs lower 50%) 1.17 ($p<0.01$).

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	8.2	7.6	0.75

Duration (years)	(4.5-12.1)	(4.2-11.6)	
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

Figure 2

Legend: 6 year survival analysis of individuals with median CBG in upper 50% (>=148.5 mg/dl) (red) vs those with IQR in lower 50% (black). 3755 matched pairs, matched for age, duration of diabetes, duration of admission, CBG IQR and number of episodes of hypoglycaemia. HR for mortality (upper vs lower 50%) 0.87

Table 2

Legend: Characteristics of case and control groups (median CBG analysis). Values given as median (IQR)

	case	control	p
n	3755	3755	
n male	1652	1617	0.39
IQR	2.3 (1.6-3.0)	2.3 (1.6-3.0)	0.86
Age	69.6 (61.1-76.9)	69.7 (61.1-77.0)	0.80
n hypoglycemic episodes	191	191	-
Diabetes Duration (years)	7.5 (3.8-11.4)	7.1 (3.5-11.1)	0.57

Admission Duration (days)	3.2 (1.6-5.8)	3.2 (1.6-5.8)	0.90
Inpatient Median Glucose	9.9 (8.9-11.5)	7.1 (6.3-7.7)	<0.001