Mortality, morbidity and temporal patterns of glycaemic measurements in populations with diabetes.

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Summary

People with diabetes mellitus account for up to 25% of a hospital population despite being only 5-8% of the general population. It has been demonstrated that the length of hospital stay and mortality is increased in patients with diabetes.
We used a database of all inpatient capillary blood glucose testing performed in Greater Glasgow and Clyde Hospitals and the national database of all patients with diabetes (SCI-diabetes) to explore the relationship between inpatient glucose outcomes. This then led to a wider exploration of temporal patterns of markers of glucose control and clinical outcome.

We analysed a large inpatient capillary blood glucose dataset to confirm that hypoglycaemia was common and particularly so overnight. We also inferred from analysis of our data that most hypoglycemia was being uncovered by routine testing and that there was a high chance of significant undiscovered hypoglycaemia. We then devised a novel metric of hypoglycaemia treatment quality (time to repeat blood glucose (TTR)). We used TTR as a marker of nationally agreed standards of care and showed poor adherence to guidelines and demonstrated that a quality improvement package could produce a sustained improvement in this metric. Our investigation of inpatient hypoglycaemia management led us to reveal that quality of hypoglycaemia care varied with the type of diabetes and diabetes treatment modality, with patient groups most at risk of harm having the least good treatment. We noticed that a highly cited paper was potentially overestimating the association between inpatient hypoglycemia and length of hospital stay as it did not take into account that the more measurement is made across a given distribution the more likely extreme results will be

found. We, therefore, used a technique which compared a mathematically modelled inpatient dataset with a real-world dataset. This confirmed the association between hypoglycaemia and length of stay remained but had been overestimated. This work enables more accurate health economic modelling of the impact of diabetes in hospital systems.

During our investigation of inpatient glucose patterns and hypoglycaemia we became interested in whether the variability of glucose per se rather than high or low glucose was clinically important. We demonstrated that inpatient glucose variability is independently associated with long term mortality. We have also confirmed the association between glucose variability patients following acute stroke and renal replacement therapy.

Our work on inpatient glucose variability led us to explore whether the variability of other longer-term indices of glucose control might be associated with poor outcome. We demonstrated an independent association between HbA1c variability and mortality in type 1 diabetes. We have since also shown that this association is independent and additive to an association between mortality and variability in visit-to-visit systolic BP. These data could be used to infer that the finding is not simply a marker of poor treatment concordance or a chaotic lifestyle. We have also shown that variability of HbA1c can be reduced by attending a structured patient education course, showing that variability of HbA1c is also a potentially modifiable risk factor for poor outcome.

Dissertation

Introduction

Diabetes mellitus is a common condition which is increasing in prevalence with an estimated growth to 366 million diagnoses worldwide by 2030. (1) Interventional trials have clearly shown an association between prolonged poor glycaemic control and the development of microvascular and macrovascular complications. (2,3)

Patients with diabetes mellitus are over represented within hospitals, accounting for up to 25% of an inpatient population despite accounting for only 5-8% of the general population. (4) While admission to hospital in this patient population may be due to complications of glycaemic control, it is often for other medical or surgical conditions. To ensure holistic patient management it is important to consider not only the management of the acute pathology leading to admission but also the management of pre-existing diabetes.

Both inpatient and long-term mortality and length of hospital stay have been unequivocally demonstrated to be increased in patients with diabetes. (4–7) This may be partially attributed to suboptimal management of underlying diabetes. (4) Glycaemic control can be destabilised by the intercurrent illness itself, making the achievement of optimal glycaemia even more challenging in the inpatient setting. (6) Whilst hyperglycemia may play a major role in the poor outcomes seen in hospitalised patients with diabetes, there is increasing recognition that iatrogenic hypoglycaemia is also an important factor. (5,6,8)

Low blood glucose (hypoglycaemia) is recognised as a major barrier to good glucose control in diabetes treated with insulin and drugs that stimulate insulin secretion. (9,10) There is an international consensus that hypoglycaemia with blood glucose levels less than 4 mmol/l should be considered an alert value to allow people with diabetes and their carers to adjust insulin or consider ingesting carbohydrate and that glucose levels of less than 3 mmol/l would indicate serious, clinically important hypoglycaemia. (11) Clinically important hypoglycaemia triggers activation of counterregulatory hormonal systems and is associated with multiple negative effects, including cardiovascular events and death. (12–17). Whilst the presence of severe hypoglycaemia has been associated with up to four times the risk of cardiovascular events and mortality causation is controversial as hypoglycaemia may be a surrogate marker for intercurrent illness or frailty. (16) Despite the possibility that hypoglycaemia is a surrogate for the general clinical state the theory that hypoglycaemia causes direct harm remains plausible as effects can be directly observed. Studies inducing hypoglycaemia have shown ECG changes including ST-segment depression, T wave inversion, prolonged QT interval and dysrhythmias. (18,19)

There has been a recognition that fluctuation in glucose levels, usually referred to as glucose variability, may also be an important factor in determining the risk of poor outcomes in diabetes over and above low and high absolute levels. The term glucose variability can have multiple definitions. Often it is thought of as the minute-to-minute and hour-to-hour changes in continuous glucose monitoring or capillary blood glucose testing which are used for treatment decision making (20).

Several studies had shown a positive association between short term glycaemic variability and macrovascular and microvascular complications of diabetes. (7,21–23)

There is also evidence that high glucose variability may be linked to a reduced feeling of well-being and lower quality of life indices. (24,25)

Glucose variability can also be used to describe variations of glucose control day-to-day or from or week-to-week.(26,27) HbA1c is a measurement of medium term glucose and is a mainstay of routine management of diabetes. A reduction of HbA1c has been shown to improve complications and mortality in both Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM). (2,3) The measurement of HbA1c is recommended in all patient with diabetes and locally has been measured in over 90% of all patient with diabetes in the preceding 15 months. (28,29)

Much as it has with short term glucose fluctuations, the variability of long term glucose control as measured by changes in HbA1c has also been shown to be associated with adverse outcomes in diabetes. HbA1c variability is known to be positively associated with an increased rate of cardiovascular events in people with T1DM with a magnitude of the impact proposed to be is at least as high as that of mean HbA1c (30,31). It has also been demonstrated that there is a positive association between visit-to-visit long term glucose control and a higher incidence of cardiovascular events in T2DM (32,33).

The existence of an increased risk of poor outcome in people with diabetes who are in hospital, and the knowledge that there are patterns of glucose which seem to be associated with harm, suggests the potential for at least some of the excess risk being modifiable. It would, therefore, be of potential benefit to be able to stratify patients on presentation to hospital for their risk of glucose characteristics associated with poor outcome. This would allow the targeting of interventions such as enhanced monitoring and specialist advice focused on improving glucose control.

Likewise, a greater understanding of the importance of variability of long term glucose fluctuations as measured by HbA1c could allow better risk stratification and identify novel targets for harm reduction.

My research over the past 6 years summarised in this dissertation and described in detail in the 9 papers accompanying this submission aim to explore these relationships.

Inpatient Hypoglycaemia

We analysed a large inpatient glucose dataset, of 3 345 241 CBG data points, to describe the trends in the timing of CBG monitoring and investigate whether these were appropriate based on observed patterns of hypoglycaemia. We confirmed that hypoglycaemia was common and occurs in 26.2% of all admissions and that it occurred especially frequently overnight with a peak in the risk of hypoglycaemia between 3 and 4 am. We also inferred from the analysis by comparing 'by the clock peaks' of measurement with nadirs of measurement frequency that most hypoglycemia was being uncovered by routine testing and that there was a high chance of significant undiscovered hypoglycaemia. (34) This paper gives useful insight into the importance of hypoglycaemia and can be used to consider a more rational and targeted CBG monitoring regime for inpatients with diabetes.

We then described a novel metric of hypoglycaemia treatment quality (time to repeat blood glucose (TTR)). We used TTR as a marker of nationally agreed standards of care and showed poor adherence to guidelines. Of 90 935 episodes of glucose <4 mmol/l

only 8.9 % had a repeated measure within 15 minutes. Median TTR was 80 minutes. TTR was shown to reduce in proportion to how low the initial measurement of CBG was suggesting that lower initial readings within the hypoglycaemic range were considered more serious. Even so, treatment was suboptimal even at very low initial CBG with median TTR of 22 minutes (IQR 10-47) for initial CBG of 1-1.9 mmol/l. We then demonstrated that a quality improvement package could produce a sustained improvement in this metric which persisted up to 9 months. (35) We believe that TTR is a simple real time metric which can be useful in audit and quality improvement for people in hospital with diabetes.

Our investigation of inpatient hypoglycaemia management also led us to investigate if the quality of hypoglycaemia care varied with the type of diabetes and diabetes treatment modality. We showed that patient groups at most potential risk of harm from hypoglycaemia, namely those on sulphonylureas and with T2DM, have the least good treatment as compared to national guideline standards. (36) This information has been used to raise awareness of the importance of hypoglycaemia in high risk groups and was used to inform a recently published quality improvement project. (37)

During our investigation of the importance of inpatient hypoglycaemia it had been of concern to us that a highly cited paper was potentially overestimating the association between inpatient hypoglycemia and length of hospital stay. (38) This paper did not take into account that the more measurement is made across a given distribution the more likely extreme results will be found. We, therefore, used a technique which compared a mathematically modelled inpatient dataset with a real world dataset. This confirmed the association between hypoglycaemia and length of stay remained but had been overestimated. After subtraction of the mathematical association of increased sample number the increased length of stay associated was lower than previously reported 0.75 addition days to stay per day with hypoglycaemia. This work enables more accurate health economic modelling of the impact of diabetes in hospital systems. (8)

Cystic Fibrosis Related Diabetes (CFRD is a common complication of Cystic Fibrosis which differs in from other types of diabetes in its goals for management and complication risks. (39) We investigated whether there was an association between hypoglycaemia, hyperglycaemia or glucose variability in insulin-treated patients with CFRD. We demonstrated that hypoglycaemia was common and associated with an increased composited endpoint of readmission to hospital or death. (40)

Glucose Variability

During our investigation of inpatient glucose patterns and hypoglycaemia we became interested in whether the variability of inpatient glucose per se rather than high or low glucose was clinically important. We demonstrated that inpatient glucose variability, expressed as IQR, is independently associated with long term mortality at a maximum of 6 years follow up. This study showed that in 3755 matched pairs those in the top 50% for IQR had significantly higher mortality ($p=<0.01$) when examined using the Cox proportional hazard model. (7) We hypothesised that this variability was likely to be a marker of post-discharge variability in view of the long term impact on mortality. These data add people with diabetes in a hospital setting to the large body of evidence showing an association between glucose variability and harm. No evidence yet exists to show that reduction of variability improves outcomes but aiming to use strategies that reduce variability where possible whilst awaiting further conclusive evidence could be considered.

We also confirmed the association between glucose variability and poor outcome exists in various populations including people having had an acute stroke and those on renal replacement therapy. (41,42)

HbA1c Variability

Our work on inpatient glucose variability led us to explore whether the variability of other longer term indices of glucose control might be associated with poor outcome. We investigated the association between HbA1c variability and mortality in type 1 diabetes. We used data from the SCI diabetes database which contains all patients with diabetes in Scotland. Of 6048 patients included for analysis over a period of 47 month period coefficient of variation (CV) above the median value hazard ratio for survival was increased to 1.47 (95% confidence interval 1.27-1.67)($p<0.001$) (43)

We then further investigated the association between mortality and variability of HbA1c by adding visit-to -visit systolic blood pressure (SBP) as a covariable. We dichotomised patients above and below median values for HbA1c CV and SBP CV creating 4 cohorts for survival analysis. (44) We demonstrated that the variability of both HbA1c and visit to visit BP were both significantly and additively associated with mortality. These finding replicated those previously seen in patients with T2DM. (45) These data could possibly suggest that the finding is not simply a marker of poor treatment concordance or a chaotic lifestyle as this would be less likely to explain an additive impact of variability in SBP and HbA1c.

Having shown that HbA1c is associated with mortality in T1DM we wished to investigate if methods used to improve overall glycaemic control might also improve variability. We investigated 1061 patients who had attended a Dose Adjustment for Normal Eating (DAFNE) course which is an evidence based structured education intervention for patients with T1DM. (46) We demonstrated that as well as reducing HbA1c variability of HbA1c as expressed as CV was significantly lower during the post DAFNE period than

prior to intervention (0.08 (IQR 0.05-0.12) reduced to 0.07 (IQR 0.05-0.10); P = 0.002), (47) These data give further support to the potential benefit of this structured education interventions on long term outcomes..

Discussion

Inpatient Control and hypoglycaemia

Patients with diabetes are over represented in the hospital inpatient population compared with the general population and account for up to 1 in 6 patients (38). Among patients with diabetes treated with insulin or sulfonylurea, the risk of hypoglycemia is often an important factor in preventing optimal glycemic control and treating hyperglycemia (5,6). In-hospital, hypoglycaemia is clearly associated with adverse patient outcomes such as increased length of stay and long term mortality. (5,6,8,38,48) A major issue is disentangling adverse outcomes of hypoglycemia, acute illness and chronic disease burden which can make it difficult to interpret inpatient data in people with diabetes who are admitted to hospital. Whilst our data has improved the understanding of the patterns of hypoglycaemia and helped quantify the potential for harm it is unlikely that data will ever categorically prove that inpatient hypoglycaemia is causative of mortality and increased resource usage. However, the observable physiological impact of hypoglycaemia on the cardiovascular system and the strong association with adverse outcomes in other settings suggests strategies to reduce inpatient and subsequent outpatient hypoglycemia are likely to be important. (15)

Variability

The study of glucose variability is hampered by a lack of agreed definition of both the timescales over which variability is measured and the measurement of variability itself.

It has been suggested that glucose variability can be broadly divided into short term (within the day or between day glucose fluctuations) and long term (between week and usually measured by HbA1c). (49,50) Increasingly measures of glucose variability are likely to reflect widespread availability of continuous glucose monitoring systems which will give the potential for the investigation of within minute variations.

Various computational methods have been used to express glycaemic variability. Standard deviation from the mean (SD) is a simple metric of dispersion of short term glucose results and is often calculated directly by CBG devices. The coefficient of variation is calculated as percentage (SD/ mean glucose) x 100. It has the advantage of being simple to calculate and is adjusted for the mean. With increasing data points available with CGM metrics such as Mean Amplitude of Glycemic Excursions (MAGE), which calculates mean differences from peaks to nadirs, and Continuous Overall Net Glycemic Action (CONGA), which integrates duration and degree of glucose excursions, have been used and may eventually be shown to better reflect risk of poor outcome. (51)

It is not clear why glucose variability might be harmful. Short term glucose fluctuations can lead to oxidative stress, endothelial dysfunction, disturbance of AKT pathways and cytokine release and are associated with an increased carotid intimal thickness and increased left ventricular mass. However, the link between glucose fluctuation and

oxidative stress is not been consistently demonstrated in people with diabetes. (21,52–55)

Glucose variability is potentially important as different therapeutic options may have differing glycemic variability profiles. Various therapeutic agents for diabetes including SGLT2 inhibitors, GLP-1 analogues, DPP-4 inhibitors, CSII and the ultraslow insulin analogue degludec, have been shown to reduce glycemic variability. (56–64)

It is notable that these findings relate to the effect of glucose variability over a short time period and may not be relevant to longer-term glucose variability as measured by HbA1c. In T2DM HbA1c variability has previously been associated with an increased risk of developing a range of poor outcomes including depression, atrial fibrillation, heart failure and increased mortality. (65–68) Patients with T1DM and greater HbA1c variability may lead more chaotic lifestyles and therefore have suboptimal risk factor management - for example, a higher risk of developing diabetic ketoacidosis (DKA) if they do not engage (30). This seems plausible as people with greater HbA1c variability are known to have more complex medical histories, lower quality of life, low socioeconomic status and lack of peer support systems (69).

The mechanisms linking BP variability to mortality is also unclear. Short term variability of blood pressure results from the interaction between intrinsic physiological, pathological and extrinsic environmental and behavioural factors many of which may be linked to poor outcomes (70,71). Longer term BP variability has been shown to be associated with increased mortality independently of mean BP and even when BP is well controlled (72,73). Longer term BP variability may represent a decreased ability to maintain homeostasis and this may adversely affect vascular tissues leading to end-organ damage (74,75).

The finding of a significant and additive association between SBP and HbA1c variability and mortality may have important clinical implications. Elevated variability may become important in the identification of at-risk people who may previously have been considered optimally managed. This may prove useful for prognostication and as an additional factor when evaluating the efficacy of any patient intervention. Future management of type 1 diabetes should perhaps focus on limiting the variability of SBP and HbA1c, as opposed to purely treating mean values to target. Our finding that DAFNE attendance can modify HbA1c variability offers hope that long term variability of glucose control is a tractable target for intervention.

Our work has added to the understanding of how temporal patterns of glucose are associated with outcomes in people with diabetes in both inpatient and outpatient populations. This will allow better targeting of care to individuals at high risk of the excess morbidity and mortality seen in populations with diabetes and suggests targets for future therapeutic intervention.

Future Research Directions

Although the association between the variability of short and long term variability of glucose and adverse outcomes is established many questions remain about the nature of this observation.

In the future, we plan to explore this further using linkage between inpatient CBG records and outpatient HbA1c records. This will allow us to explore whether short variability in hour-to-hour CBG is related to long term month-to-month variability in HbA1c. We would also like to use the increasing availability of data from flash glucose monitoring systems to explore the relationship between minute-to-minute glucose estimations and longer-term measures of variability.

Another area of interest moves beyond variability and looks at trajectories of measures of glucose control. This would explore whether particular patterns (e.g low to high or high to low) are the major drivers of association with variability and poor outcome.

We have also increasing looked to machine learning techniques to allow a more accurate understanding of the relationship between multiple measures over time. Recurrent neural networks (RNN) with a Long short-term memory (LSTM) architecture classify according to sequences of values within a time series and may provide a valuable tool to better predict the risk of adverse outcome. We plan to use a neural network containing convolutional (CNN) and recurrent (RNN/LSTM) layers to treat both glycaemic control and other routinely recorded data (e.g BP and weight) as a multidimensional time series, in which the sequence of values over time and the interactions between values within time series is examined.

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Corrections To Published Papers

Jones, Gregory C., Zhou M. Chong, Jennifer Gilmour, Christine Matheson, Gordon MacGregor, and Christopher A. R. Sainsbury. 2016. “Patterns and Impact of Hypoglycemia, Hyperglycemia, and Glucose Variability on Inpatients with Insulin-Treated Cystic Fibrosis-Related Diabetes.” Diabetes Therapy: Research, Treatment and Education of Diabetes and Related Disorders 7 (3): 575–82.

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Fig. 2 Survival analysis time *to first readmission or 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

Timmons, Joseph G., Scott G. Cunningham, Christopher A. R. Sainsbury, and Gregory C. Jones. 2016. “Inpatient Glycemic Variability and Long-Term Mortality in Hospitalized Patients with Type 2 Diabetes.” Journal of Diabetes and Its Complications, June. https://doi.org/10.1016/j.jdiacomp.2016.06.013.

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Fig. 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 *(p<0.01)*.