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HbA_{1c} variability is associated with increased mortality and earlier hospital admission in people with Type 1 diabetes

Short title: HbA_{1c} variability and mortality in Type 1 diabetes

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What's new?

- HbA_{1c} variability is known to be associated with mortality in Type 2 diabetes.
- This is the first study to show an association between HbA_{1c} variability and mortality in Type 1 diabetes.
- Our data also show an association between HbA_{1c} variability and the combined end-point of death or first admission to hospital.
- HbA_{1c} variability could be a useful clinical marker of risk in people with Type 1 diabetes.

Abstract

Aim Despite evidence of morbidity, no evidence exists on the relationship between HbA_{1c} variability and mortality in Type 1 diabetes. We performed an observational study to investigate whether the association between HbA_{1c} variability and mortality exists in a population of people with Type 1 diabetes. As a secondary outcome, we compared onset of first hospital admission between groups.

Methods People with Type 1 diabetes were identified for inclusion from the Scottish Care Information – Diabetes data set. This database includes data of all people known to have diabetes who live within Scotland. A survival analysis was carried out over a 47-month period comparing two groups; group 1 with a HbA_{1c} coefficient of variation (CV) above the median CV value, and group 2 with a CV below the median value. Time to death or first admission was also analysed. A Cox proportional hazard model was used to compare time to death, adjusting for appropriate covariables.

Results Some 6048 individuals with Type 1 diabetes were included in the analysis. Median HbA_{1c} CV was 7.9. The hazard ratio (HR) for mortality for those with an HbA_{1c} CV above the median value is 1.5 over 47 months of follow-up ($P < 0.001$). HR for survival to either the first admission to hospital or death for those with an HbA_{1c} CV above the median value was 1.35 (95% confidence interval 1.25–1.45) over 730 days of follow-up ($P < 0.001$).

Conclusion Our results show that people with greater HbA_{1c} variability have a higher rate of mortality and earlier hospital admission in Type 1 diabetes.

Introduction

HbA_{1c} is an essential measurement used in the management of Type 1 diabetes. The Diabetes Control and Complications Study (DCCT) showed that intensive glycaemic control as measured by HbA_{1c} reduces microvascular complications [1]. Follow-up of this cohort

revealed that earlier lowering of HbA_{1c} leads to a reduced incidence of cardiovascular disease, with the effect persisting for up to 30 years [2].

The term glucose variability can have multiple definitions. Most commonly it is thought of as the minute-to-minute and hour-to-hour changes in continuous glucose monitoring (CGM) or capillary blood glucose (CBG) testing which are used for real-time treatment decision-making [3]. The term can also be used to describe variations of glucose from day-to-day or week-to-week [4].

One marker of longer term, month-to-month, glucose variability is fluctuation between HbA_{1c} measures. In Type 2 diabetes greater HbA_{1c} variability has been consistently associated with microvascular complications and linked with increased frequency of cardiovascular events and all-cause mortality, independent of baseline HbA_{1c} [4–8]. For measurement of HbA_{1c} variability, studies have either used a standard deviation (SD) or coefficient of variation (CV). Both SD and CV are measures of variability. SD measures how much values differ from the group mean, whereas CV is the ratio of SD to the mean. There is no agreed standardised method of measuring HbA_{1c} variability [8].

In Type 1 diabetes the DCCT did not uncover an association between short-term glucose variability and increased risk of microvascular complications, as measured via SD [9,10]. By contrast, longer term HbA_{1c} variability in Type 1 diabetes, also measured via SD, was shown to predict the development of retinopathy and nephropathy over and above the mean HbA_{1c} value [10,11]. The DCCT used 3-monthly seven-point glucose profiles equivalent to 28 finger-stick measurements per year, which may not have been enough data to adequately assess glycaemic variability. However, increased incidence of cardiovascular events has also been associated with increased HbA_{1c} variability in Type 1 diabetes, with the magnitude of the impact proposed to be at least as high as that of mean HbA_{1c} [11,12].

Despite evidence of morbidity, no firm evidence exists of the relationship between HbA_{1c} variability and mortality in Type 1 diabetes. We aimed to investigate whether the association exists in a population of people with Type 1 diabetes, as previously described in Type 2 diabetes. As a secondary outcome, we also looked at onset of first hospital admission.

Methods

Patients coded as having Type 1 diabetes and appearing on 1 January 2013 in the Scottish Care Information Diabetes (SCI-Diabetes) data set in Greater Glasgow and Clyde were considered for inclusion. SCI-Diabetes is a database containing data for all people known to have diabetes living in Scotland. A diagnosis of diabetes at least 12 months prior to a 30-month run-in period was required. This period was chosen to reduce the potential confounding effect of a likely sudden reduction of glucose immediately post diagnosis. All HbA_{1c} measurements made during the run-in period were identified. The number of measurements made was recorded, along with the median HbA_{1c} and CV of identified HbA_{1c} measurements. The age of participants at 1 January 2013 was calculated; all included participants were >13 years old at this time point.

Mortality data (date of death) were available within the SCI-Diabetes data set. Time of the first hospital admission post 1st January 2013 was inferred from the hospital CBG data set, comprising data from all eight hospitals in the health board area. CBG value, time of test, date of test and corresponding patient identifier was extracted from analysis of the Abbott Precision Webb system (Abbott, Maidenhead, UK). A hospital admission was defined as a patient with more than two CBG measurements undertaken within 5 days. CBG data were available to 5 January 2015.

Survival analysis

To assess potential associations between HbA1c CV and mortality we used a proportional hazards regression (Cox) model. Potential confounding risk factors included were diabetes duration (years), median HbA_{1c} during the run-in period, total number of HbA_{1c} measurements made during run-in and age at 1 January 2013. The hazard ratio (HR) was used to estimate the relative risk of death during the follow-up period. Analysis was performed using the coxph function within the R package 'survival'.

Time to death or first admission

A survival analysis (as described above) was performed over the period 1 January 2013 to 5 January 2015, investigating time to the competing endpoints of either admission to hospital or death. Potential confounding risk factors included were diabetes duration (years), median HbA_{1c} during the run-in period, total number of HbA_{1c} measurements made during run-in and age at 1 January 2013.

Results

Some 6048 individuals with Type 1 diabetes were included in the analysis. Median HbA_{1c} CV was 7.9 (interquartile range (IQR) 5.1–11.8). Characteristics of analysed groups above and below this median CV are shown in Table 1.

Survival analysis

The survival plot is shown in Fig. 1. HR for mortality for those with an HbA_{1c} CV above the median value is 1.47 (95% confidence interval (CI) 1.27–1.67) over 1430 days of follow-up ($P < 0.001$).

Time to first hospital admission or death

HR for survival to first hospital admission or death for those with an HbA_{1c} IQR above the median value is 1.35 (95% CI 1.25–1.45) over 730 days of follow-up ($P < 0.001$), using identical covariables as above (Fig. 2).

Discussion

Previous studies have shown increased mortality in people with Type 2 diabetes who have higher HbA_{1c} variability [4–8]. Although it is known that HbA_{1c} variability increases microvascular complications in Type 1 diabetes there is no previous evidence of increased mortality in this group [10]. Our results demonstrate increased mortality and earlier hospital admission associated with HbA_{1c} variability in Type 1 diabetes.

There is no accepted standard measure of variability of HbA_{1c}. We have chosen to use CV because this measure is calculated using both mean and SD. CV therefore intrinsically mitigates to some extent the influence of average HbA_{1c} on variability.

The potential mechanisms of our observations are uncertain. *In vitro* studies have shown that short-term glucose fluctuations induce more oxidative stress than continuous high glucose [13]. Endothelial dysfunction is precipitated due to the release of inflammatory cytokines progressing to increased carotid intimal thickness and increased left ventricular mass [14]. The impact of glucose variability and oxidative stress in humans is less clear [15,16]. Although some studies have shown a positive correlation, alternative studies have failed to find a link [13,17]. It must be remembered that these studies can only look at the effect of glucose variability over a short interval. Furthermore, there is no firm evidence that short-term glucose variability progresses to longer term glucose variability. Therefore, short-term glucose fluctuations may be irrelevant when considering morbidity and mortality.

HbA_{1c} variability could be a marker of variable treatment concordance. Patients with greater variability may lead more chaotic lifestyles and therefore have suboptimal management, for example, a higher risk of developing diabetic ketoacidosis if they do not engage [12]. Greater HbA_{1c} variability is also associated with reduced medication compliance and the use of antipsychotics and glucocorticoids which may impair glycaemic control [6]. Other associations with greater HbA_{1c} variability are more complex medical histories, lower quality of life, low socio-economic status and lack of peer support systems [6]. Therefore, perhaps these risk factors lead to higher levels of morbidity and mortality.

Disease processes that could lead to both improvement or worsening of HbA_{1c} variability are worth further consideration. These could act as confounding variables between HbA_{1c} and mortality. An example is a hypothetical patient who develops renal failure and a change in HbA_{1c} measurement due to reduced insulin clearance.

The main strength of our study is analysis of an inclusive database with a large cohort of patients over a long observation. The main weakness is that we cannot be certain of causation. Further research is required to ascertain whether HbA_{1c} variability causes poor health outcomes directly or whether confounding factors such as concurrent renal disease, smoking, social deprivation or use of lipid- and blood pressure-lowering medications might be influencing the observed increase in mortality. Unfortunately, robust data on these potential confounding factors was not available for analysis. Treatment with continuous subcutaneous insulin infusion (CSII) has been shown to reduce cardiovascular mortality [18]. As of June 2015, only 7.1% of adults with Type 1 diabetes in Scotland were using CSII treatment [19]. Over the time course of this study, this percentage will have been significantly lower. It is therefore unlikely that CSII usage would have had a major impact on outcomes. Analysis of whether HbA_{1c} variability leads to increased incidence of specific causes of

death, for example diabetic ketoacidosis has not been carried out. It would be useful to analyse this in more detail in future studies.

This is the first study to demonstrate a relationship between HbA_{1c} variability and mortality in people with Type 1 diabetes. Our results may have clinical implications. Although guidelines stress the importance of tight glycaemic control, this may not be appropriate in some populations [20]. Rapid improvements in glucose control have been associated with worsening of clinical outcome. In an inpatient cardiothoracic population, improvement in glycaemic control, and potential increased HbA_{1c} variability, led to worse outcome in patients with diabetes [21].

Perhaps glycaemic metrics beyond single time-point HbA_{1c} could be implemented as more effective measures for assessing risk of an individual developing diabetes complications [22]. With progression of technology allowing direct monitoring of blood glucose fluctuations, assessment of the efficacy of diabetes mellitus treatment can move forward from HbA_{1c} measurement as the sole marker of glycaemic control [23]. Even if HbA_{1c} variability in Type 1 diabetes has a non-causal association with poor outcomes it allows for effective risk stratification and identification for intervention.

In conclusion, our results show that people with greater HbA_{1c} variability have a higher rate of mortality and earlier hospital admission in Type 1 diabetes. Limiting HbA_{1c} fluctuations over time may reduce these risks. It is important to note that people may have suboptimal control of their diabetes despite having a 'well controlled' HbA_{1c}. Identification of patients with high variability of HbA_{1c} may be beneficial by allowing for targeting of support and increased education by the specialist diabetes team.

Funding sources

Competing interests

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References

1 The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; **329**: 977–986.

2 Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular outcomes in Type 1 diabetes: the DCCT/EDIC study 30-year follow-up. *Diabetes Care* 2016; **39**: 686–693.

3 McCall AL, Kovatchev BP. The median is not the only message: a clinician's perspective on mathematical analysis of glycemic variability and modeling in diabetes mellitus. *J Diabetes Sci Technol* 2009; **3**: 3–11.

4 Zoppini G, Verlato G, Targher G, Bonora E, Trombetta M, Muggeo M. Variability of body weight, pulse pressure and glycaemia strongly predict total mortality in elderly type 2 diabetic patients. The Verona Diabetes Study. *Diabetes Metab Res Rev* 2008; **24**: 624–628.

5 Prentice JC, Pizer SD, Conlin PR. Identifying the independent effect of HbA1c variability on adverse health outcomes in patients with Type 2 diabetes. *Diabet Med*

2016; 33: 1640–1648.

6 Ma W-Y, Li H-Y, Pei D, Hsia T-L, Lu K-C, Tsai L-Y *et al*. Variability in hemoglobin A1c predicts all-cause mortality in patients with type 2 diabetes. *J Diabetes Complicat* 2012; **26**: 296–300.

7 Skriver MV, Sandbæk A, Kristensen JK, Støvring H. Relationship of HbA1c variability, absolute changes in HbA1c, and all-cause mortality in type 2 diabetes: a Danish population-based prospective observational study. *BMJ Open Diabetes Res Care* 2015; **3**: e000060.

8 Gorst C, Kwok CS, Aslam S, Buchan I, Kontopantelis E, Myint PK *et al*. Long-term glycemic variability and risk of adverse outcomes: a systematic review and meta-analysis. *Diabetes Care* 2015; **38**: 2354–2369.

9 Lachin JM, Bebu I, Bergenstal RM, Pop-Busui R, Service FJ, Zinman B *et al*. Association of glycemic variability in type 1 diabetes with progression of microvascular outcomes in the Diabetes Control and Complications Trial. *Diabetes Care* 2017; **40**: 777–783.

10 Kilpatrick ES, Rigby AS, Atkin SL. A1C variability and the risk of microvascular complications in type 1 diabetes: data from the Diabetes Control and Complications Trial. *Diabetes Care* 2008; **31**: 2198–2202.

11 Wadén J, Forsblom C, Thorn LM, Gordin D, Saraheimo M, Groop P-H *et al*. A1C variability predicts incident cardiovascular events, microalbuminuria, and overt diabetic nephropathy in patients with type 1 diabetes. *Diabetes* 2009; **58**: 2649–2655.

12 Kilpatrick ES. The rise and fall of HbA(1c) as a risk marker for diabetes complications.

Diabetologia 2012; **55**: 2089–2091.

13 Siegelaar SE, Holleman F, Hoekstra JBL, DeVries JH. Glucose variability; does it matter? *Endocr Rev* 2010; **31**: 171–182.

14 Di Flaviani A, Picconi F, Di Stefano P, Giordani I, Malandrucco I, Maggio P *et al*. Impact of glycemic and blood pressure variability on surrogate measures of cardiovascular outcomes in type 2 diabetic patients. *Diabetes Care* 2011; **34**: 1605–1609.

15 Monnier L, Mas E, Ginet C, Michel F, Villon L, Cristol J-P *et al*. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA* 2006; **295**: 1681–1687.

16 Ceriello A, Esposito K, Piconi L, Ihnat MA, Thorpe JE, Testa R *et al*. Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. *Diabetes* 2008; **57**: 1349–1354.

17 Wentholt IME, Kulik W, Michels RPJ, Hoekstra JBL, DeVries JH. Glucose fluctuations and activation of oxidative stress in patients with type 1 diabetes. *Diabetologia* 2008; **51**: 183–190.

18 Steineck I, Cederholm J, Eliasson B, Rawshani A, Eeg-Olofsson K, Svensson A-M *et al*. Insulin pump therapy, multiple daily injections, and cardiovascular mortality in 18,168 people with type 1 diabetes: observational study. *BMJ* 2015; **350**: h3234.

19 Scottish Diabetes Survey Monitoring Group. Scottish Diabetes Survey 2015. Available at http://diabetesinscotland.org.uk/Publications/SDS2015.pdf Last accessed 17 June 2014.

20 Tseng C-L, Soroka O, Maney M, Aron DC, Pogach LM. Assessing potential glycemic overtreatment in persons at hypoglycemic risk. *JAMA Intern Med* 2014; **174**: 259–268.

21 Greco G, Ferket BS, D'Alessandro DA, Shi W, Horvath KA, Rosen A, et al. Diabetes and the association of postoperative hyperglycemia with clinical and economic outcomes in cardiac surgery. *Diabetes Care* 2016; **39**: 408–417.

22 Bergenstal RM. Glycemic variability and diabetes complications: does it matter? Simply put, there are better glycemic markers! *Diabetes Care* 2015; **38**: 1615–1621.

23 Kovatchev BP. Metrics for glycaemic control – from HbA1c to continuous glucose monitoring. *Nat Rev Endocrinol* 2017; 13: 425–436.

FIGURE 1 Time to death over 47 months of follow-up for 6048 individuals with Type 1 diabetes. Solid line, individuals with an HbA_{1c} coefficient of variation (CV) below the median value of 7.9. Dashed line, individuals with an HbA_{1c} CV above the median value.

FIGURE 2 Survival to first admission or death over 47 months for 6048 individuals with Type 1 diabetes. Solid line, individuals with an HbA_{1c} coefficient of variation (CV) below the median value of 7.9. Dashed line, individuals with an HbA_{1c} CV above the median value.

Table 1 Characteristics of groups with HbA_{1c} coefficient of variation (CV) above and below median value.

	HbA_{1c} CV		
	< 7.9	≥ 7.9	*P*-value
n	3024	3024	
Mean age at 1 January 2013 (years)*	44.0 (16.9)	42.9 (18.5)	< 0.01
Median no. of HbA_{1c} measurements during run-in period†	4 (3–5)	4 (3–5)	0.45
Mean HbA_{1c} during the run-in period (mmol/mol; %)†	72.4; 8.8 (16.4)	74.8; 9 (17.1)	< 0.01
Median diabetes duration (years)*	19.0 (11.9–29.0)	16.2 (9.7–27.0)	< 0.01
No. of deaths during follow-up period	168	246	< 0.01
No. of admissions or deaths during follow-up period	693	865	< 0.01

Comparisons between groups were made using the Mann–Whitney *U* test.

Values in parentheses are *SD or †IQR.