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REVIEW

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Glucose variability measures and their effect on mortality: a systematic review

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Abstract *Objective:* To systematically review the medical literature on the association between glucose variability measures and mortality in critically ill patients. *Methods:* Studies assessing the association between a measure of glucose variability and mortality that reported original data from a clinical trial or observational study on critically ill adult patients were searched in Ovid MEDLINE® and Ovid EMBASE®. Data on patient populations, study designs, glucose regulations, statistical approaches, outcome measures, and glucose variability indicators (their definition and applicability) were extracted. *Result:* Twelve studies met the inclusion criteria; 13 different indicators were used to measure glucose variability. Standard deviation and the presence of both hypo- and hyperglycemia were the most common indicators. All studies reported a statistically significant association between mortality and at least one glucose variability indicator. In four studies both blood glucose levels and severity of illness were considered as confounders, but only one of them checked model assumptions to assert inference validity. *Conclusions:* Glucose variability has been quantified in many different ways, and in each study at least one of them appeared to be associated with mortality. Because of methodological limitations and the possibility of reporting bias, it is still unsettled whether and in which quantification this association is independent of other confounders. Future research will benefit from using an indicator reference subset for glucose variability, metrics that are linked more directly to negative physiological effects, more methodological rigor, and/or better reporting.

Keywords Blood glucose · Blood glucose variability · Glycemic control · Mortality · Systematic review

Introduction

Glucose control aiming at normoglycemia, i.e., blood glucose levels (BGLs) of 80–110 mg/dl, which is frequently referred to as "tight glycemic control" (TGC), decreased morbidity and mortality of critically ill patients [1]. Later studies investigated the effect of various forms of glucose control on mortality and morbidity and reported that no beneficial effects of these interventions were found [2–5]. Some studies showed that their implementation of glucose control with insulin comes with the risk of hypoglycemia [6, 7], others did not [8, 9].

Partly in order to reconcile the findings of these seemingly contradictory results, confounders—correlating with both blood glucose levels and mortality—and other possible factors associated with mortality were sought. One of these potential confounders or possible factors associated with mortality is blood glucose variability, which in essence quantifies the spread in a set of blood glucose levels.

The underlying idea for considering glucose variability is that it, similar to hyperglycemia, can be associated with mortality by increasing oxidative stress, neuronal damage, mitochondrial damage, and coagulation activity [10–13]. It has been shown that rapid fluctuations of BGLs increase oxidative stress and are more detrimental than sustained hyperglycemia. In consequence, investigating the role of blood glucose variability as a new target in blood glucose control was suggested [13, 14]. However, one may distinguish between various sources of variability in BGLs. The variability can be relatively controllable, induced by intervention, or its can effectively appear random (e.g., due to patient condition changes). All variability that exposes the patient to negative physiological consequences is to be avoided.

The main objective of this systematic review was to identify and summarize published studies on glucose variability and their association with mortality in critically ill patients. This summary includes an overview of all the glucose variability indicators used along with a methodological examination of the studies. This review may form a basis for future developments of a standard list of well-defined glucose variability indicators and methodological considerations thereby contributing to the comparability and quality of new studies.

Materials and methods

We searched for relevant English-language articles based on keywords in title, abstract, and MeSH terms, using Ovid MEDLINE®, Ovid MEDLINE® In-Process (1950 to April 30, 2010) and Ovid EMBASE® (1980 to April 30, 2010). The final literature search was performed on May 10, 2010.

Figure 1 shows the search strategy. Searching was supplemented by scanning bibliographies from identified articles. Two authors independently examined all titles and abstracts. Discrepancies among the two authors were resolved by consensus involving a third author. Articles were included if they reported original data from a clinical trial or observational study on critically ill patients and concerned the association between glucose variability and mortality. Opinion papers, surveys, and letters were excluded.

From the selected papers, the same two authors extracted data on the patient population, study design, glucose regulation, statistical approach, outcome measures, and glucose variability indicators (their definition and applicability). Discrepancies between the two authors were again resolved by consensus after involving the

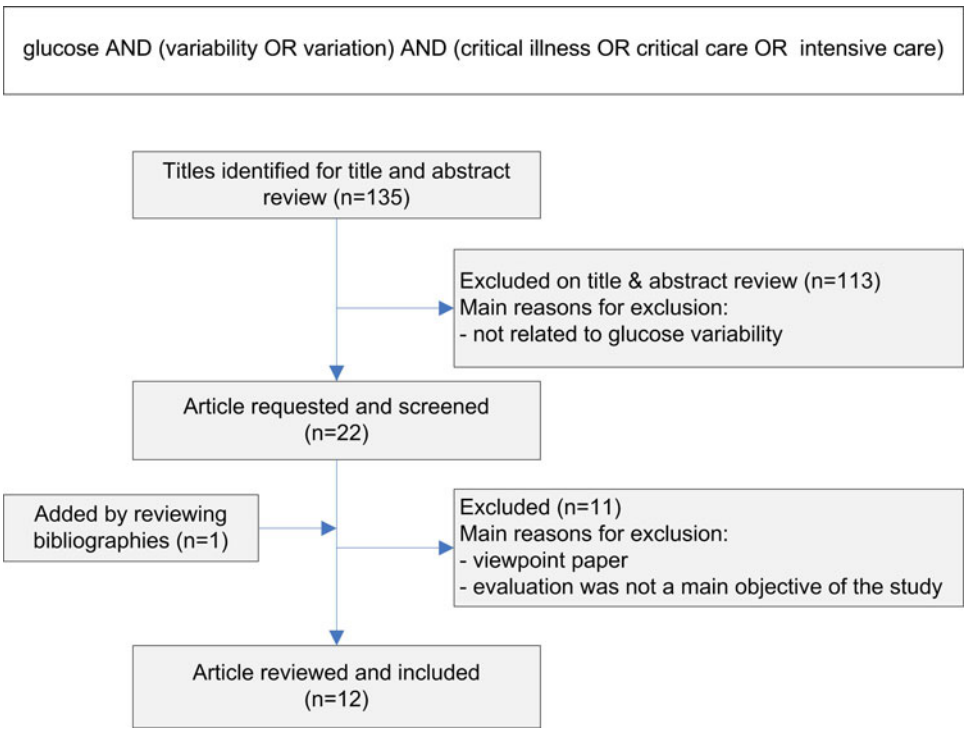

Fig. 1 The search flow diagram

same third author. Heterogeneity of the retrieved studies in terms of the extracted data (patient populations, study designs, variability indicators etc.) was informally assessed to determine whether a meta-analysis was justified.

Results

Searching the online databases resulted in 135 articles. Initial screening of titles and abstracts rendered 22 articles eligible for further full-text review. Inspecting the bibliographies of these articles yielded an extra article. On the basis of the full-text review, 11 studies, including the one added by the bibliographic search, were excluded, leaving 12 articles for detailed analysis. Table 1 uniformly describes these studies.

Table 2 lists and describes the 13 glucose variability indicators used. The most frequently used indicator was the standard deviation (SD) of BGLs per patient, which was employed in 6 out of 12 articles. Five out of six studies reported on a statistically significant positive association between SD and mortality. The populations in these studies were sepsis patients (2/6) and mixed surgical and medical patients (4/6).

The second commonly used indicator is what we call the "hyper–hypo" indicator which is a binary (true or false) variable defined as true for a patient having both hyperglycemia and hypoglycemia measurements during some predefined interval. Two interval-variants of the hyper–hypo indicator were encountered in 3/12 studies: one variant was defined for the whole intensive care unit (ICU) admission and the other for the first 24 h after admission. Two of the three studies using the hyper–hypo indicator showed a statistically significant association with mortality and the third study reported consistent but non-significant association. However, six different thresholds were used in these three studies for defining hyperglycemia (>150, >180, and >216 mg/dl) and hypoglycemia (<60, <72, and <81 mg/dl). The study populations were also different in these studies and included patients with brain injury, mixed medical/surgical patients, and non-diabetic patients receiving insulin during their admission.

Each of the rest of the eleven indicators was used in only one study. All of them were found to be statistically significantly associated with ICU and/or hospital mortality.

In the majority of studies the association between mortality and the used variability indicator was adjusted for by using linear logistic regression analysis (Table 1). However, different sets of possible confounders were used. Six out of 12 studies used at least one severity of illness indicator as a confounder in the final regression model. Only four studies included the mean or median BGL as a confounder in the final regression model. In four studies both blood glucose levels and severity of illness were considered as confounders. All studies assumed a linear relationship between (log odds of) mortality and either the blood glucose variability indicator itself or the confounders used, but only one study reported on testing this assumption [15]. A more recent study [16] showed that observed mortality reduction with intensive insulin therapy (IIT) in the original Leuven trials could not be attributed to blood glucose variation defined by SD and mean daily δ blood glucose. However that study also showed that increased blood glucose variation was associated with mortality irrespective of blood glucose level. Protocol implementation (with or without IIT) and level of adherence to it either were not mentioned or differed from one study to another. In addition, different BGL target ranges were used in the studies that reported on adherence.

Discussion

The apparent heterogeneity of the retrieved studies does not justify conducting a meta-analysis. Although all 12 studies reported a significant association between mortality and one or more of a set of 13 glucose variability indicators, the study heterogeneity, the methodological limitations, and the possibility of reporting bias do not support an unequivocal evidence for the independence of this association of other factors, let alone its causal nature. To our knowledge, this is the first review of the literature on the association between blood glucose variability and mortality. Because of the current attention to blood glucose variability in critically ill patients, we believe the review to be timely, enabling the dissemination of the lessons learned from the reviewed studies. A limitation of our search is that we only addressed studies that had a main objective of evaluating the association between mortality and glucose variability; we might have missed some studies with a limited focus.

Aside from differences in patient case-mix and in the associated therapy, the diversity of the variability indicators used, and the fact that only few if at all were used together, hampers comparability of the studies and hence of the consolidation of evidence. In addition, and especially because none of the studies had an randomized control trial (RCT) design, one cannot a priori exclude the possibility of a reporting bias, in which only indicators showing associations in a study were reported.

BGL distributions are not necessarily normally distributed nor even symmetric about the mean, especially as the physiologically reported variations are also not necessarily normally distributed. Yet, many studies report variability in terms of, e.g., standard deviation. Inference

Table 1 Summary of reviewed studies

Reference	Patient population and location(s)	Variability indicator(s)	Outcome measure	Glucose regulation	Statistical approach	Results	Reported conclusion
Meyfroidt et al. [16], 2010, Belgium	2,748 adult patients, 56-bed surgical and 17-bd medical ICU	SD Mean daily δ BGL	Hospital mortality	Nurse driven With protocol TR1 <16 TR2 80–110 M 4 h (at max)	Univariate analysis and multivariate logistic regression adjusted for admission category, malignancy, gender, body mass index, age, admission BGL For mixed medical/surgical patients: mean morning BGL > 110 versus ≤110, at least one episode of hypoglycemia (<40) and SD or mean daily δ BGL Only medical patients: hyperglycemia index, BGL pattern irregularity, and SD or mean daily δ BGL	Intensive insulin therapy significantly increased the mean daily δ BGL (72 vs. 59 mg/dl). There was no significant effect on the SD of the BGL. In adjusted multivariable logistic regression analysis the following variables were independently associated with hospital mortality: BGLs outside the normoglycemic range, higher mean daily blood glucose, higher standard deviation blood glucose	Increased blood glucose amplitude variation was associated with mortality, irrespective of blood glucose level
Hermanides et al. [13], 2010, Netherlands	5,728 patients, with more than 2 BGL measurements, 18-bed mix ICU	SD MAG	Hospital mortality	Arterial whole blood sampling Nurse driven With IIT protocol and CDSS TR 72–126 M 15 min–4 h	Univariate analysis and multivariate logistic regression adjusted for MAG quartile, sex, age, diabetes mellitus, severity of disease (maximal SOFA score), severe hypoglycemia event, mean BGL, and cardiothoracic surgery	The ORs for ICU death were higher for quartiles of MAG compared with quartiles of mean glucose or SD. The highest OR for ICU death was found in patients with the highest MAG in the upper glucose quartile: OR 12.4 (95% CI 3.2– 47.9; $p < .001$). Mortality rates were lowest in the lowest MAG quartiles	High glucose variability is firmly associated with ICU and hospital mortality
Jacka et al. [25], 2009, Canada	606 patients with brain injury, 64% post operation, 11-bed neurological ICU	Hyper–hypo	Hospital mortality	Finger capillary sampling Nurse driven With protocol 12.4% of patients with IIT protocol	Univariate analysis and multivariate logistic regression adjusted for age, sex, diagnostic category, diabetes mellitus, presence of IIT	BG variability occurred in 3.8% of IIT patients and with median number of 13 hypo- and hyperglycemia episodes per patient. BG variability was not associated with a significant increase in crude and adjusted odds of hospital mortality but the rate of recurrence of hypo- and hyperglycemia episodes showed significant associations with mortality (adjusted OR 1.04, 95% CI 1.00–1.08)	BG variability showed non-significant but consistent associations with hospital mortality

Table 1 continued

Reference	Patient population and location(s)	Variability indicator(s)	Outcome measure	Glucose regulation	Statistical approach	Results	Reported conclusion
Bagshaw et al. [26], 2009, Australia, NewZealand	66,184 patients, first 24 h of admission, 24 ICUs	Hyper–hypo	ICU and hospital mortality	Whole blood sampling <10% of patients with IIT protocol	Univariate analysis and multivariate logistic regression adjusted for ICU location, age, sex, co-morbidity, non age related APACHE II, surgical status, primary diagnosis, MV, acute kidney injury, and year	BG variability was associated with greater odds of adjusted ICU (1.5, 95% CI 1.4–1.6) and hospital (1.4, 95% CI 1.3–1.5) mortality, when compared with hypoglycemia alone	Early variability in BG is relatively common and independently portends an increased risk for mortality
Pidcoke et al. [27], 2009, US	49 patients with severe burns	The percent excursion above and below target	Mortality	Finger capillary sampling Nurse driven With protocol TR 80–110 M 1 h	Univariate analysis	Individual average variability was 50 ± 8%. Percent excursions in those with high compared with low variability scores was 56 ± 6% versus 43 ± 5% ($p = 0.001$). Mortality in the highly variable group was twice that of the less variable group (50 vs. 22%, $p = 0.041$)	High glucose variability (defined as >50% of values outside the 80–110 range) is associated with increased mortality
Dossett et al. [28], 2008, US	858 ventilated surgical and trauma patients with at least 5 measurements, surgical and trauma ICU	Blood glucose percentile Triangular index Successive change in BGL SD	Hospital mortality	Physician/nurse driven With protocol and CDSS TR 80–110 M 1–2 h	Univariate analysis and multivariate logistic regression used to compare combination of percentiles. Patients were assigned to group based on BGL percentile	SD for those with similar mean BGL and percentile values of BGL did not significantly differ between survival status groups. The mean largest successive increases (and decrease) in BGL were 54 mg/dl (and −71 mg/dl) for survivors and 70 mg/dl (and −79 mg/dl) for nonsurvivors, with $p = 0.001$ (and $p = 0.02$). The maximum absolute change was 76 mg/dl versus 94 mg/dl ($p = .005$). The triangular index for all measures was statistically different between the two groups	Increased blood glucose variability in terms of triangular index and successive change in BGL is associated with mortality
Hirshberg et al. [29], 2008, US	863 non-diabetic patients, hypoglycemia event should not be reason for ICU admission, without insulin administration, >24 h stay, ≤18 years, 26-bed pediatric ICU	Hyper–hypo	Mortality	Without protocol	Univariate analysis in different mean BGL groups (<60, 60–150, >150). Multivariate logistic regression adjusted for PRISM III, medical diagnosis group	BG variability occurred in 6.8% of all patients. It was statistically significantly associated in univariate and multivariate analysis with increased mortality (OR 63.6; 95% CI 7.8–512 and OR 40.5; 95% CI 4.6–358.7)	BG variability in the multivariate analysis was associated with increased mortality

Table 1 continued

Reference	Patient population and location(s)	Variability indicator(s)	Outcome measure	Glucose regulation	Statistical approach	Results	Reported conclusion
Krinsley [19], 2008, US	3,252 adult patients, 14-bed mixed medical/surgical ICU	SD	Hospital mortality	Finger capillary sampling + plasma glucose (tested in central lab) Nurse driven Non-IIT (before 2003) and IIT protocol (from 2005) TR 80–140 and 80–125	Univariate analysis in different mean BGL groups (70–99, 100–119,120–139, 140–179, 180+). Multivariate logistic regression adjusted for age, APACHE II without the age component, MV, SD of mean BGL, diabetic status, treatment era (non-IIT and IIT), and different groups of mean BGL (70–99, 100–119,120–139)	Quartile with highest variability had 5-, 3-, 2-, and 1.7-fold increase in mortality versus the lowest quartile for patients with mean BGL between 70–99, 100–119, 120–139, and 140–179 mg/dl (all $p \leq 0.01$). Multivariable analysis demonstrated that GV independently conferred increased risk of mortality among patients with mean BGL up till 39 mg/dl (in all cases $p \leq 0.05$)	Increasing glycemic variability conferred a strong independent risk of mortality
Waeschle et al. [30], 2008, Germany	191 patients with sepsis, severe sepsis or septic shock, 42-bed ICU	SD	ICU and hospital mortality	Finger capillary sampling Nurse driven With two different protocols TR 80–140 M 30 min–3 h	Univariate analysis and multivariate logistic regression adjusted for rate of severe hypoglycemia (≤40), median SD, present of IIT protocol	Multivariate analyses showed a significant association of SD levels with critical hypoglycemia especially for patients in septic shock ($p = 0.0197$). In addition, SD levels above 20 mg/dl were associated with a significantly higher mortality rate relative to those with SD levels below 20 mg/dl (24 vs. 2.5%, $p = 0.0195$)	Significant association of SD levels with critical hypoglycemia was shown. In addition SD levels were associated with mortality rate
Ali et al. [15], 2008, US	1,246 septic patients hospitalized for more than 1 day	SD MAGE GLI	Hospital mortality	Whole blood glucose Plasma glucose (tested in central lab)	Multivariable logistic regression adjusted for number of organ failure, occurrence of hypoglycemia, insulin administration, frequency of glucose monitoring and capillary testing Because of significant interaction between the glucose-related measures, the subjects were divided into four groups (median and IQR) based on GLI and mean BGL	MAGE, SD, and GLI were associated with hospital mortality (crude OR 1.12, 1.16, 1.25, $p < 0.001$ in all cases) and, GLI had the best AUC (59, .62, .67, $p < 0.001$). GLI was not independently associated with mortality for those with mean BGL > median. Subjects with increased GLI, but lower mean BGL had almost 5-fold odds of hospital mortality than those with lower GLI (OR 4.73, 95% CI 2.6–8.7)	MAGE, SD, and GLI were associated with hospital mortality. GLI had the best discrimination for mortality

Table 1 continued

Reference	Patient population and location(s)	Variability indicator(s)	Outcome measure	Glucose regulation	Statistical approach	Results	Reported conclusion
Egi et al. [31], 2006 Australia	7,049 patients Diabetes diagnosis data was available in 2 out of 4 ICUs, 4 surgical/ medical mixed ICUs	SD Relative variability	ICU and hospital mortality	Whole blood sampling Nurse driven Without protocol TR 108–180	Univariate analysis and multivariate logistic regression adjusted for ICU location, age, APACHE II, category of ICU admission, surgical/ medical admission, SD, mean BGL, max BGL, admission BGL, MV, and diabetes status	The mean ± SD of SD was 30 ± 23 versus 41 ± 29 mg in survivors versus nonsurvivors ($p < 0.001$). Both mean and SD of blood glucose were significantly associated with ICU mortality [$p < 0.001$; adjusted OR (per 18 mg) 1.23 and 1.27] and hospital mortality [$p < 0.001$ and $p = 0.013$; OR (per 18 mg) 1.21 and 1.18]	The SD of BGLs is a significant independent predictor of ICU and hospital mortality
Wintergerst et al. [32], 2006, US	1,094 <22 years old non-diabetic patients, pediatric ICU	Glucose variability index	Hospital mortality	Whole blood glucose Plasma glucose (tested in central lab)	Univariate analysis and multivariable logistic regression adjusted for glucose variability, minimal BGL, and maximal BGL	Mortality rate with highest versus lowest quintile was 15.1 versus 1.3% ($p < .0001$). Glucose variability, minimal glucose level, and maximal glucose level (all with $p \leq 0.05$) each had an independent relationship with death	Glucose variability was associated with mortality rate

Except for reference [30], which reported on a prospective observational cohort, all studies pertained to retrospective observational cohorts. Unit of all BGL thresholds is mg/dl

BGL blood glucose level, *SD* standard deviation, *GLI* glycemic lability index, *MAG* mean absolute glucose, *MAGE* mean amplitude of glycemic excursions, *CI* confidence interval, *ICU* intensive care unit, *IIT* intensive insulin therapy, *LOS* length of stay, *M* monitoring, *MV* mechanical ventilation, *OR* odds ratio, *TR* target range, *AUC* area under the curve, *IQR* interquartile range, *GV* glycemic variability, *CDSS* computerized decision-support system

Table 2 List of applied blood glucose variability indicators

Variability indicators	Definition	Ref.
Standard deviation	SD of BGL measurement for each patient during the complete stay in ICU or during the first 24 h after admission [31]	[13, 15, 16, 19, 30, 31]
Both hypo and hyper	Defined for a patient as any patient as the presence of both hyperglycemia (>150 [29], >180 [25], or >216 mg/dl [26]) and hypoglycemia (<60 [29], <72 [25], or <81 mg/dl [26]) during the complete stay in ICU [25], [29], or during the first 24 h after ICU admission [26]	[25, 26], 29]
Blood glucose percentile	Individual variable ranked, with various percentiles (P50, P95, etc.)	[28]
Glucose variability index	Mean of absolute difference of sequential BGLs divided by the difference in BGL collection time	[32]
GLI	Squared difference between consecutive BGLs per unit of actual time between those samples	[15]
MAG	Mean absolute glucose change per patient per hour	[13]
MAGE	Mean of absolute values of any delta BGL (consecutive values) that are >1 SD of the entire set of BGLs	[15]
Mean daily δ BGL	Mean of daily difference between minimum and maximum BGL	[16]
Relative variability	Coefficient of variability ($Glu_{CV} = Glu_{SD} \times 100/Glu_{Ave}$)	[31]
Successive change	Successive change in BGL calculated by determining the difference in two consecutive BGLs—the largest successive increase, decrease, and absolute value were calculated for each patient (regardless of interval between measures)	[28]
Percent excursion above and below target	Percent excursion (as fraction of the whole) above and below BGL target with the total number of measurements as the denominator	[27]
Triangular index	Calculated by dividing the maximum sample density distribution of each histogram for BGL (i.e., the mode) from an individual patient (on a discrete scale with bin of 1 mg/dl) by the total number of each measurement	[28]

BGL blood glucose level, *GLI* glycemic lability index, *MAG* mean absolute glucose, *MAGE* mean amplitude of glycemic excursions

based on normality assumptions may then be flawed as they, e.g., would imply the existence of negative BGLs below a number of standard deviations from the mean. The variability itself in exposure to hyper- or hypoglycemia may as well not be symmetric about a mean value. Application of normal statistics to lognormal or skewed distributions can hence yield misleading results.

There should be an agreement on which subset of indicators should be used and reported in future studies but this requires a better understanding of what the indicators intend to measure. This is particularly relevant because the act of measuring BGL is primarily directed to inform future BGL regulation decisions, so BGL measurements would tend to cluster around changes. Some changes are beneficial because they steer BGL towards a target value, others are not. If indicators do not take the direction of a change into account, as is the case, e.g., for the mean absolute glucose (MAG), mean amplitude of glycemic excursions (MAGE), and glycemic lability index (GLI), then they are likely to be sensitive to the sampling frequency of the blood glucose regulation policy and there is a possibility that they, indirectly, also reflect severity of illness. MAG, MAGE, and GLI take order of measurements into account but only MAG and GLI consider the time that elapsed between measurements. SD, hypoglycemia, hyperglycemia, mean daily δ BGL, and successive change do not take order and timing of measurements into account. Both hypo- and hyperglycemia also depend on the defined threshold. It is unclear which characteristics are responsible for picking up on the variability with the true deleterious biological effect and which are not. To the best of our knowledge there is no study that measured correlation among measures of variability. This merits future research and it can shed light on what is missed when using one measure rather than another.

Recently we suggested that the association of measures such as MAG with mortality may well be blurred by the frequency of observations, and in turn by whether the patients belong to a TGC cohort or not [17]. Three studies [16, 18, 19] investigated the association between mortality and variability in a TGC and/or a control group as well as in a pooled cohort. In contrast to the Leuven study [16], the SPRINT study [18] showed no significant association between variability and mortality in the SPRINT or TGC arm. Krinsley et al. [19] showed that treatment in the TGC era was negatively correlated to SD. TGC might in this sense be perceived as statistically "decoupling" metrics of variability from mortality within a TGC cohort. Further similar analyses are recommended. In addition, one should realize that there are two statistical ways to view association: testing and estimation. Testing pretends that the answer to the association question is yes or no. In contrast,

in estimation one simply attempts to quantify the strength of the association, however weak it may be. "Proving" the absence of any association is very hard, but it is easy to quantify its strength. There is a need for new statistical approaches, such as the Bayesian approach, that do not rely on p values and testing, and this facilitates more reliable meta-analysis.

A recent study [20] performed complexity analysis in glycemia time series and showed that loss of complexity, evaluated by detrended fluctuation analysis, is associated with higher mortality. Lack of complexity may signify failure of regulatory systems or extreme consequences of pathophysiological processes. It might be useful to perform complexity analysis, in addition to the traditional variability analysis, in future studies.

Although the majority of studies used linear logistic regression to adjust for confounders, different sets of candidate confounders were used in the studies, again hampering comparability. The choice of these candidates should be motivated by the possible explanations of the suspected association between glucose variability and mortality. Egi et al. [12] state that there are at least three possible explanations for this association. First, less glucose variability could result from more attention in medical and nursing care. Second, less glucose variability may be associated with less severity of illness. Third, glycemic variability might have a true deleterious biological effect in critically ill patients. Hence it is important to always control for the measurement rate per patient (influenced by the blood glucose control protocol and the severity of illness of the patient) as well as severity of illness itself. Otherwise the true deleterious biological effect will be blurred. It is hence beneficial to report on the relationship between a variability indicator and factors that may influence it including measurement rate (or mean interval between measurements) and severity of illness. This was not attempted in the studies. Aside from adjustment in the model, the assumption of linearity between (log odds of) mortality and the indicator and/or the confounders used was not tested when the variables were coded as continuous. By making sure that the assumptions hold, one gets unbiased odds ratio estimates of the variables used.

The course taken in research pertaining to the association between blood glucose variability and mortality is reminiscent of the course taken in researching the association between blood glucose level indicators and the quality of the glucose regulation process. In two recent systematic reviews we showed that many different and even ambiguous quality indicators were used to measure the quality of glucose regulation in these studies which hinders synthesizing evidence [8, 21, 22]. If blood glucose variability is to form a new target in blood glucose control, we need to acknowledge that the term covers various types of variability and define at this stage a uniform set of quality indicators for it that can be used consistently and compared in each study to avoid reporting bias. Second, if some indicators are unambiguously shown to be associated with mortality then we need to develop an approach for influencing them. However this is not trivial especially because other factors, such as mean blood glucose level, should be reckoned with. These important issues should be addressed before conducting new clinical trials on blood glucose variability.

Finally, glycemic metrics in TGC are typically only linked to mortality through a host of other therapies and factors (such as patient condition and age). Linking mortality and glycemia may, however, simply be a "bridge too far" as there is no direct physiological link between glycemia and mortality, except through a range of intermediate physiological processes, which may or may not tip the balance. What seems useful is to have a metric of variability (or level) that links between glycemic control and a clinical outcome that is "closer" to the physiological effects of glycemia than mortality. This link has appeared in some studies [23, 24]. Seeking metrics that are linked more directly to negative physiological effects merits further research.

Conclusion

The evidence about the independent association between BGL variability and mortality is still unsettled, partly because the term variability bears different meanings and partly because of heterogeneity of studies, design, and methodological and reporting limitations.

All the following considerations separately and combined can benefit future research. The first is an RCT design to investigate the effect of strategies specifically targeting glucose variability reduction on mortality. However, it is hard to implement an intervention that could randomize patients to different variability cohorts, holding other glycemic outcomes equal. It might be acceptable to acknowledge that our understanding is likely to come from observational data. The second is a better understanding of what these different indicators measure and their relationship to the perceived quality of the BGL regulation process, the sampling frequency, and direction of change of BGLs. The third is a uniform indicator reference subset for glucose variability. The fourth is a better methodology and reporting practice, including adjustments and assumption checking pertaining to confounders and reporting association measures between severity of illness, measurement rates, and the variability indicators.

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