www.jmscr.igmpublication.org
Impact Factor 5.84
Index Copernicus Value: 83.27
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v5i7.239

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Original Article

Glycaemic variability and Mortality in critically ill patients

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Background
Critical illness is still a major part of burden on healthcare systems and comprises about 7.6% of total in-hospital admissions[1]. Critically ill patients have different glucose metabolism due to stress related conditions, an entity labeled as stress hyperglycemia which is mainly attributed to release of counter regulatory hormones[2,3]. Stress hyperglycemia is found in both diabetic as well as non-diabetics moreover in non- diabetics[4]. Fasting blood sugar, postprandial blood sugar, HbA1c are important predictors of glycemic control. But these have limitations in critical set up and thus there is one more entity beyond these traditional markers i. e. glycemic variability (GV)[3] which may be an important predictor of outcome in critically ill patients.
The definition of glycemic variability is the intraday glycemic excursions including episodes of hyper and hypoglycemia[5]. The concept of glucose variability is more complex phenomenon because it introduces the idea that multiple fluctuations of glucose in the same individual could be more harmful than a simple episode of acute hyperglycemia or, indeed, chronic stable hyperglycemia[6]. GV is a physiological phenomenon that takes on an even more important dimension in the presence of diabetes and during critical illness as it is important prognostic marker for survival in this subset of patients[7]. This prospective cohort study was done to investigate whether glycemic variability is associated with increased mortality in critically ill patients with or without diabetes.

Materials and methods
Study design
This was a prospective hospital based cohort study carried out in a tertiary care hospital during the period of January 2014 to October 2015. Based on

previous studies we kept absolute precision of 8%, assuming 95% confidence interval and the sample size was calculated to be 111. Accordingly, we included 110 patients in our study.

Study participants

110 consecutive cases admitted in MICU (Medical Intensive Care Unit) of our hospital with a systemic early warning score; SEWS > 3 were enrolled in the study. APACHE II score was also calculated for each patient. The variables for Apache II score were determined by history and well defined standard criteria. Other variables like hematocrit, white blood cell count, Serum creatinine were obtained by lab investigations. Serum electrolytes and arterial blood gases were obtained by analysis of arterial blood on Cobas 221 blood gas analyzer by Roche. (A-a) gradient was calculated using alveolar gas equation PAO_2 = (FiO_2* (760-47))- ($PaCO_2$/0.8) and (PAO_2 – PaO_2).Diabetes mellitus was defined as per ADA 2014 criteria. Patients with surgical cause for critical illness, trauma, diabetic ketoacidosis and hyperosmolar non-ketotic coma, starvation ketosis, infective hepatitis and those dying within 48 hours of hospitalization were excluded from the study.

On admission Blood Glucose levels and HbA1c, serum creatinine, sodium, potassium and arterial blood gas analysis were done. 4 hourly capillary blood glucose monitoring was done using a calibrated Acuchek sensitive glucometer in MICU for first 48 hours and 1 venous blood glucose value (randomly) was estimated in local laboratory. Minimum 8 values were taken for each patient. Standard treatment was continued for all patients as per the decision of treating physicians. There was no specific insulin protocol followed in our MICU. Hence treatment of diabetes and hyperglycaemia was as per treating physicians' decisions. The patients were followed up till discharge or death. The primary outcome measure of the study was all cause mortality. The secondary outcome measure was presence or absence of diabetes.

Glycaemic variability parameters

We used Standard Deviation(SD), Coefficient of Variation(CV) and Mean Amplitude of Glycaemic Excursion(MAGE) as parameters of glycaemic variability which were calculated using the predefined formulae.

Statistical analysis

Continuous variables were compared in between by performing independent t test for normalized data and Mann-Whitney Rank Sum test for non-normalized data. Categorical variables were analysed by Pearson's Chi square test and Chi square for trend linear data. Multiple logistic regression analysis was performed to analyse the independent effects of mean blood glucose and S.D. on mortality. Receiver operating characteristic (ROC) was used to determine the best cut off for parameters of glycaemic variability with statistical software STATA version 13.0 for data analysis.

Results

Out of 110 cohorts,50 (45.5%) patients were in the survivor group and 60 (54.5%) in the non survivors group. There were 60 (54.5%) patients with diabetes of which 43(71.7%) died and 17(28.3%) were survivors. 22.7% patients were in the age group of 41-50 years, mean age was 46.55 + 16 years. The mean age of survivors was 48.95+ 17.1 and non survivors was 44.47+ 15 years. The M: F was 1 :0.9 and mortality was similar in both genders. Of the comorbidities, hypertension was present in 44.5% patients and IHD in 37.5 % patients with no significant difference for outcome. The baseline characteristics of all patients are shown in Table 1. Severity of illness as determined by Apache II score was a highly significant factor for mortality. Higher APACHE II scores>14, mean score = 25.38 + 5.69, were associated with increased mortality and lower APACHE II scores <14, mean score = 13.97 + 4.61 were associated with increased survival.

In survivors admission blood glucose was 149.57 ± 37.08 mg/dl and innon-survivors it was 170.37

± 43.46 mg/dl, thus higher mean admission blood glucose was associated with increased mortality (p= 0.0064, HS). The mean of MBG (Mean Blood Glucose)in survivors was 153.40 ± 34.95 mg/dl and it was 168.17 ± 43.97 mg/dl in non survivors and the difference was statistically non-significant (p = 0.0556,NS). However, there was a significant difference for various ranges of MBG as calculated. It was observed that mortality was high when MBG was < 100 mg/dl or > 180 mg/dl with high survival in euglycemic range of MBG (100-144 mg/dl) (Figure 1).

We used three parameters for glycemic variability i.e. Standard Deviation (SD), Coefficient of Variation (CV) and Mean Amplitude of Glycemic Excursion (MAGE) with best cut offs calculated as per area under ROC.

SD and CV of mean blood glucose (as parameter of glycemic variability) were significantly increased in patients who died as compared to survivors. As compared to reference MAGE of 0-36 mg/dL, patients who have MAGE > 72 mg/dL have 6.57 odds of dying. As mean amplitude of glycemic excursion (MAGE) increased, mortality was also increased in significant manner(Table 2). Standard deviation (SD) was divided in quartiles for each subpopulation of mean blood glucose and values of which are depicted in the(Figure 2).

Even when SD is matched with specific range of MBG, mortality increases as value for SD increases, implying that more the glycemic variability, more is the mortality in critically ill patients. On further analysis, after dividing SD into deciles and comparing with mortality, the increasing trend was confirmed.

Out of 110 patients, 16 patients had 1 episode of hypoglycemia and 8 cases had 2 episodes of hypoglycemia. Of survivors, single episode was observed in 6 (15%) compared to 10 (14.3%) in non survivors. Similarly, 2 episodes of hypoglycemia were present in only 5% of survivors and 8.6% in mortality group. The difference was statistically not significant. As we had very few episodes of hypoglycemia with no episode of severe hypoglycemia, hypoglycemia did not have effect on in-hospital mortality in critically ill patients.

Out of 110 patients, 60 (54.5%) were diabetic and 50 (45.5%) were non diabetic and there was no significant difference for in hospital mortality as far as diabetic status was considered. The duration and treatment of diabetes also had no significant impact upon mortality. Diabetic non survivors had increased glycemic variability as compared to diabetic survivors. We determined HbA1c level for each patient and found that HbA1c which is an indicator of long term glycemic control in diabetics is a significant predictor of morality in critically ill diabetic patients.

In diabetic patients, non survivors had higher admission blood glucose;231.37 ± 95.64 mg/dl as compared to survivors;190.7 + 66.8 mg/dl. The difference was statistically not significant, p= 0.1146. But when glycemic variability was studied, SD and MAGE of mean blood glucose were significantly higher in diabetic patients who died as compared to survivors.

Multiple logistic regression, revealed that APACHE II score, admission blood glucose and glycemic variability (SD) were independent predictors of mortality. As we found that APACHE II score could be major confounding factor affecting mortality in critically ill patients, we adjusted for the same and found that all three parameters of glycemic variability i.e. S.D., C.V. and MAGE were significantly associated with mortality even after adjusting for APACHE II as a major confounding factor(Table 3 and Figure 3).

Table 1: Baseline characteristics of all patients

SN	Baseline Characteristic	Survivors (n=40)	Non Survivors (n=70)	p-value
1	Age (years)	48.95 ± 17.18	44.47 ± 15.04	0.2346, NS
2	M: F	1 : 0.8	1 : 1.05	0.5250, NS
3	Comorbirdities			
	Hypertension	20(50%)	29(41.4%)	0.3934, NS
	Coronary artery disease	15(37.5%)	21(30%)	0.429, NS
	Stroke	5(12.5%)	7(10%)	0.6886, NS
	COPD	5(12.5%)	15(21.4%)	0.2561,NS
	Tuberculosis	5(12.5%)	10(14.3%)	0.8146, NS
	Other	12(30%)	20(28.5%)	0.1432, NS
4	Apache II			
	0-14	25 (96.2%)	1(3.8%)	**< 0.0001, HS**
	15-20	10(52.7%)	9(47.3%)	
	21-34	5(8.7%)	53(91.3%)	
	>34	Nil	7(100%)	
	Mean Score	13.97 ± 4.61	25.38 ± 5.69	

Table No.2 : Glycaemic Variability in Survivors and Non survivors

Measure of glycemic variability	**Cut off**	**Survivors (n=40)**	**Non Survivors (n=70)**	**Odds ratio, 95% C.I., p-value, significance**
Standard deviation(SD)	>49 (n=62)	11(27.5%)	51(72.9%)	OR=6.46, C.I.2.55 – 16.77, p<0.0001,HS
	≤ 49 (n=48)	29(72.5%)	19(27.1%)	
Coefficient of variation(CV)	>32 (n=59)	10(25%)	49(70%)	OR=7.0, C.I.2.69 – 18.77, p<0.0001,HS,
	≤ 32 (n=51)	30(75)%	21(30%)	
MAGE	0-36 (n=44)	25(56.8%)	19(43.2%)	-
	37-54 (n=29)	8(27.6%)	21(72.4%)	3.45, 1.13 – 10.93, p= 0.0141, S
	55-72 (n=25)	5(20%)	20(80%)	5.26, 1.50 – 20.79, p= 0.0030, HS
	> 72 (n=12)	2(16.7%)	10(83.3%)	6.57, 1.15 – 66.54, P=0.0136, S

Table No 3 The Effect of Adjustment for APACHE II score on statistical significance of predictors of mortality.

Variable	**Unadjusted model**			**Adjusted for APACHE II score model**		
	Odds ratio	**95% C.I.**	**p value**	**Odds ratio**	**95% C.I.**	**p value**
Admission blood glucose	2.68	1.18-6.05	0.017	4.82	1.44-16.16	0.010
Mean blood glucose	4.21	1.83-9.65	<0.001	2.83	0.99-8.04	0.052
HbA1c	4.24	1.79-10.01	<0.001	2.63	0.91-7357	0.07
S.D.	7.07	2.96-16.91	<0.001	6.68	2.19-20.36	<0.001
C.V.	6.99	2.90-16.86	<0.001	11.31	3.32-39.63	<0.001
MAGE	4.47	1.95-10.24	<0.001	3.2	1.13—9.04	0.028

Figure 1 : Correlation of Mean blood glucose with Mortality

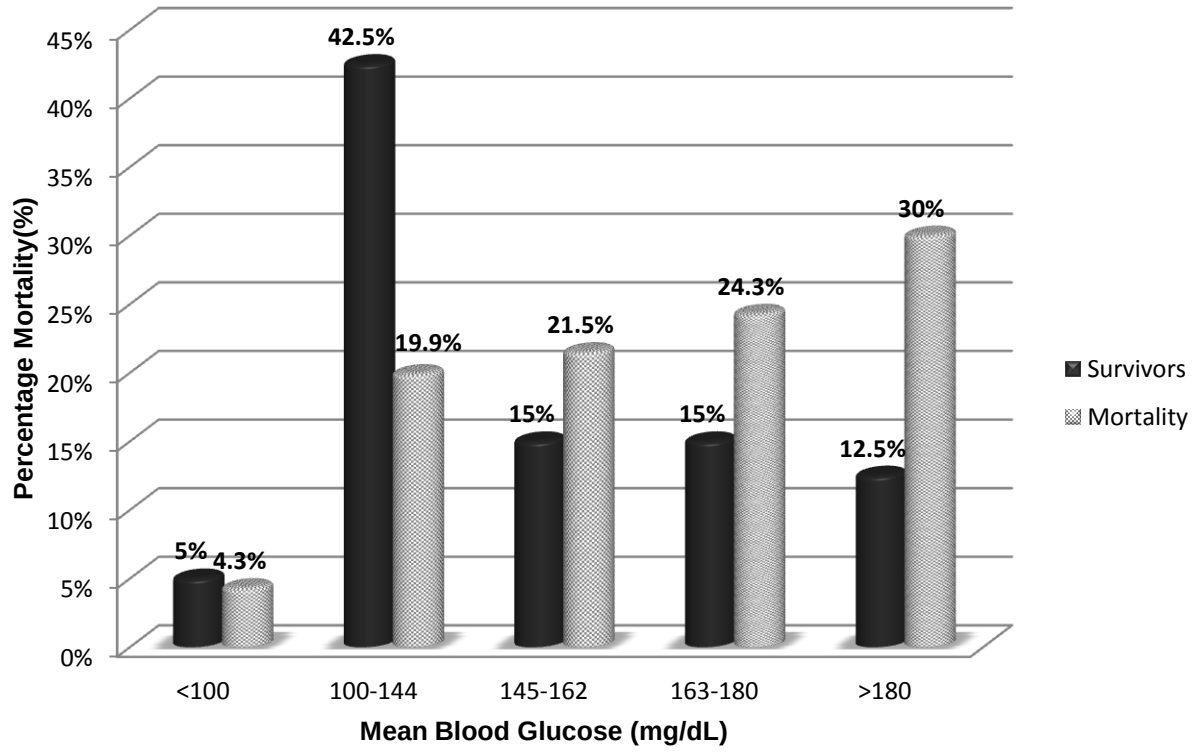


Figure 2 : Mortality according to Quartiles of increments of Mean blood Glucose. Q1 represents lowest and Q4 represents highest quartile of Glycaemic variability

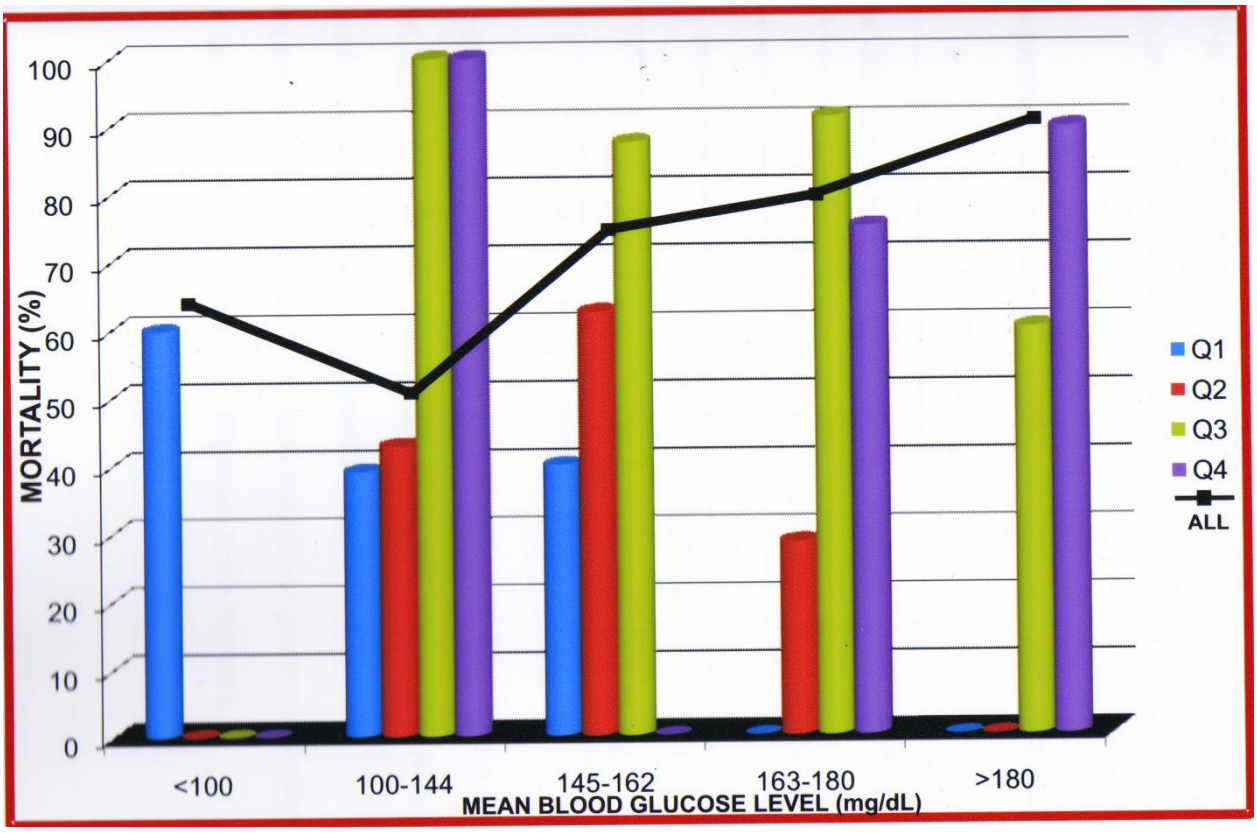
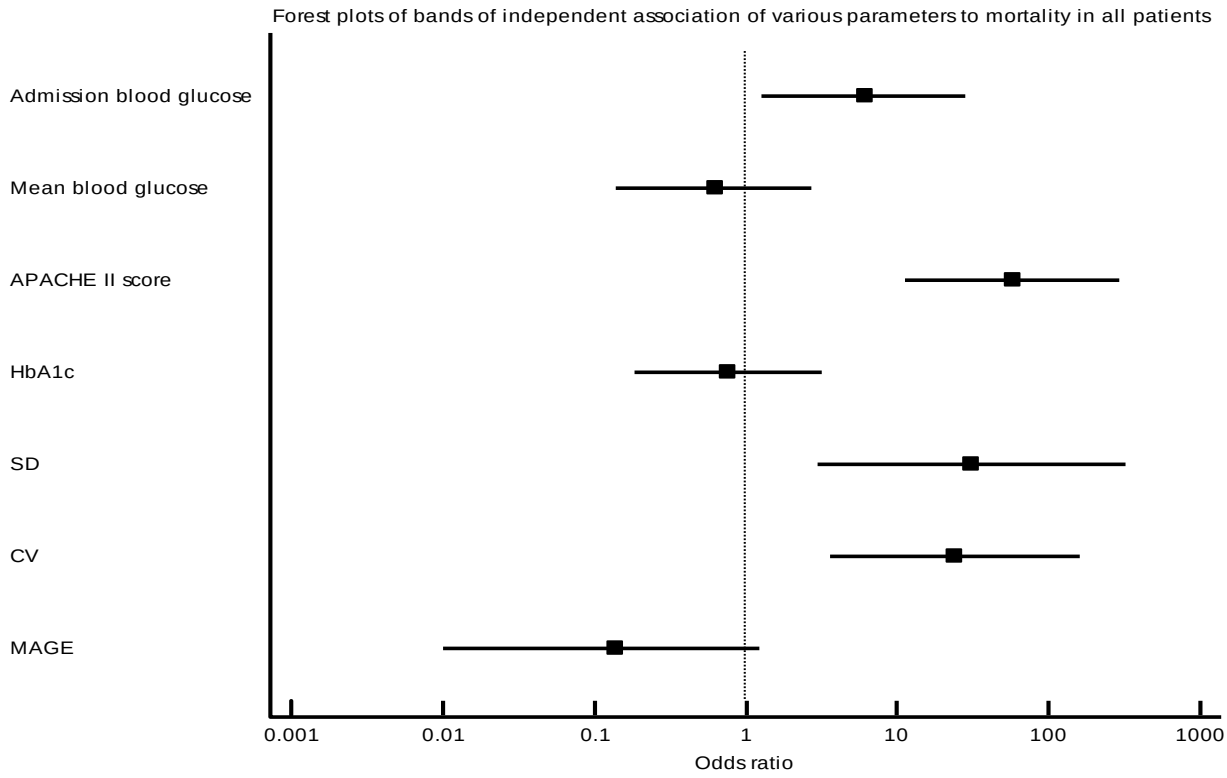


Figure 6 : Independent predictors of mortality in critically ill patients



Discussion

In literature, few studies have been done till now using different parameters of glycemic variability. Egi M et al[8] observed that survivors had mean SD of 30.6 ± 23.4 mg/dL and non-survivors had mean SD of 41.4 ± 28.8 mg/dL implying more glycemic variability in decedents. Todi S et al[9] also observed same results for SD of mean blood glucose. For coefficient of variation as a parameter of glycemic variability comparable results were observed in Verona diabetes study[10]. When MAGE was used as a parameter of GV Zhang J et al[11] and Su G et al [12] observed comparable results. We observed increased proportionate mortality in 3rd and 4th quartiles of SD, the results which were consistent with study of Krinsley JS et al[13]. Ali et al [14] analyzed SD, GLI and MAGE of mean blood glucose in cohort of critically patients of sepsis and came to same conclusion. There are at least 4 possible explanations for association of GV and outcome. Swings in glucose levels may have biological toxicity. First, less glycemic variability may reflect a more attention to detail in medical and nursing care, which may improve outcome. Second, less GV may be associated with less severe illness. Third, GV may have deleterious effect on tissues. Fourth, combination of all above factors. We also observed that Glycaemic variability was associated with increased mortality in critically ill patients after controlling for major cofounding factor i.e. APACHE II score. In diabetic patients, also GV was associated with increased mortality after controlling for HbA1C levels. The association of HbA1c with mortality and increased GV with mortality can be taken as an evidence to link GV with glycaemic control. GV should be an important parameter to assess glycemic control in diabetic patients. We observed that SD, CV and MAGE all three parameters are significantly and independently associated with increased mortality in critically ill patients, across all ranges of mean blood glucose. Refuting the findings of previous studies, we found that GV to be significantly associated with mortality in diabetics also. Glycemic Variability represents a new therapeutic target of glycemic control which needs to be treated using appropriate insulin

protocols in ICU which should also be individualized.

The strengths of our study includeit to be one of the very few studies on Glycemic Variability (GV) from India, prospective nature of data collection with protocolized frequency of testing blood glucose in specialized Medical Intensive Care Unit of tertiary care hospital and sub analysis of Glycemic Variability in diabetic patients, also. The limitations of our study include time bound study with relatively small sample size and being a tertiary care center, more severely ill patients with a higher APACHE II score were admitted, resulting in increased overall mortality in the cohort.

Conclusions

To conclude, Glycaemic Variability as determined by Standard Deviation, Coefficient of Variation and Mean Amplitude of Glycaemic Excursion is an independent predictor of mortality in critically ill patients after controlling for Admission blood glucose, Mean blood glucose and APACHE II score. Glycemic variability is significantly associated with mortality in diabetics also after controlling for HbA1c.

Implications

Along with fasting blood glucose, post-prandial blood glucose and glycated hemoglobin (HbA1c), Glycemic Variability (GV) is an important parameter of glycemic control which must be targeted, especially in critically ill patients. Specific insulin protocols should be developed to minimize Glycemic Variability in Intensive Care Unit.

Compliance with Ethical Standards:

Funding: This study was Self-funded and Support from Institute

Conflict of Interest: No conflict of interest declared by any of the authors

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Institutional ethics committee.

Informed consent: Informed consent was obtained from all individual participants included in the study.

References

1. Kahn JM, Le T, Angus DC, et al. The epidemiology of chronic critical illness in the United States. *Crit Care Med* 2015 Mar; 43(2):282–7.
2. McCowen KC, Malhotra A, Bistrian BR. Stress-induced hyperglycemia. *Crit Care Clin*. 2001 Jan; 17(1):107-24.
3. Kota S, Modi K, Satya Krishna S. Glycemic variability: Clinical implicate-ons. *Indian J Endocr Met*. 2013; 17(4):611
4. Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. *Mayo Clin Proc*. 2003; 78(12):1471-8.
5. Raz I, Wilson PW, Strojek K, et al. Effects of prandial versus fasting glycemia on cardiovascular outcomes in type 2 diabetes: The HEART 2D trial. *Diabetes Care* 2009; 32:381-6.
6. Hirsch IB, Brownlee M. Should minimal blood glucose variability become the gold standard of glycemic control? *J Diabetes Complications*. 2005; 19(3):178–81.
7. Krinsley JS. Glycemic variability: a strong independent predictor of mortality in critically ill patients. *Crit Care Med* 2008; 36:3008–13.
8. Egi M, Bellomo R, Stachowski E, et al. Blood glucose concentration and outcome of critical illness: the impact of diabetes. *Crit Care Med*. 2008; 36(8):2249-55.
9. Todi S, Bhattacharya M. Glycemic variability and outcome in critically ill. *Indian J Crit Care Med*. 2014; 18(November):285–90.

10. Muggeo M, Zoppini G, Bonora E, et al. Fasting plasma glucose variability predicts 10-year survival of type 2 diabetic patients: the Verona Diabetes Study. *Diabetes Care*. 2000; 23(1):45–50.
11. Zhang J-W, He L-J, Cao S-J, et al. Effect of glycemic variability on short term prognosis in acute myocardial infarction subjects undergoing primary percutaneous coronary interventions. *Diabetol Metab Syndr*. 2014; 6(1):76.
12. Su G, Mi S, Tao H, Li Z, et al. Impact of admission glycemic variability, glucose, and glycosylated hemoglobin on major adverse cardiac events after acute myocardial infarction. *Diabetes Care*. 2013; 36(4):1026–32.
13. Krinsley JS. Glycemic variability: a strong independent predictor of mortality in critically ill patients. *Crit Care Med* 2008; 36:3008–13.
14. Ali NA, O'Brien JM Jr, Dungan K, et al. Glucose variability and mortality in patients with sepsis. *Crit Care Med*. 2008; 36(8): 2316–21.