

# Relationship between glycated hemoglobin, Intensive Care Unit admission blood sugar and glucose control with ICU mortality in critically ill patients

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## Abstract

**Background and Aims:** The association between hyperglycemia and mortality is believed to be influenced by the presence of diabetes mellitus (DM). In this study, we evaluated the effect of preexisting hyperglycemia on the association between acute blood glucose management and mortality in critically ill patients. The primary objective of the study was the relationship between HbA<sub>1c</sub> and mortality in critically ill patients. Secondary objectives of the study were relationship between Intensive Care Unit (ICU) admission blood glucose and glucose control during ICU stay with mortality in critically ill patients. **Materials and Methods:** Five hundred patients admitted to two ICUs were enrolled. Blood sugar and hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) concentrations on ICU admission were measured. Age, sex, history of DM, comorbidities, Acute Physiology and Chronic Health Evaluation II score, sequential organ failure assessment score, hypoglycemic episodes, drug history, mortality, and development of acute kidney injury and liver failure were noted for all patients. **Results:** Without considering the history of diabetes, nonsurvivors had significantly higher HbA<sub>1c</sub> values compared to survivors ( $7.25 \pm 1.87$  vs.  $6.05 \pm 1.22$ , respectively,  $P < 0.001$ ). Blood glucose levels in ICU admission showed a significant correlation with risk of death ( $P < 0.006$ , confidence interval [CI]: 1.004–1.02, relative risk [RR]: 1.01). Logistic regression analysis revealed that HbA<sub>1c</sub> increased the risk of death; with each increase in HbA<sub>1c</sub> level, the risk of death doubled. However, this relationship was not statistically significant ( $P: 0.161$ , CI: 0.933–1.58, RR: 1.2). **Conclusions:** Acute hyperglycemia significantly affects mortality in the critically ill patients; this relation is also influenced by chronic hyperglycemia.

**Keywords:** Blood sugar, critically ill patients, glucose control, hemoglobin A<sub>1c</sub>, mortality

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## Introduction

Diabetes of injury has been shown to result in increased mortality rates during critical illness,<sup>[1-3]</sup> necessitating targeted blood glucose control according

to numerous international guidelines, irrespective of the presence of diabetes mellitus (DM).<sup>[4-6]</sup> Perioperative blood glucose control also decreases morbidity and mortality in critically ill patients.<sup>[7,8]</sup> Interestingly, acute

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hyperglycemia (induced by stress), hypoglycemia, and glycemic variability have been found to be poor prognostic factors in various subsets of critically ill patients including trauma patients. Therefore, it seems that the impact of acute hyperglycemia on outcome depends on premorbid glycemia control. Recent studies indicate that the association between hyperglycemia and outcome could be influenced by the presence of chronic hyperglycemia, and they have suggested that optimal blood glucose concentration might be higher in these patients.<sup>[9-11]</sup> Thus, the risk of decreasing blood sugar with insulin therapy during Intensive Care Unit (ICU) stay could be increased; which is related to the severity of hyperglycemia within the previous 2-3 months. It has been estimated that each 1% augmentation in hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) concentrations is associated with 15-20% greater cardiovascular risks.<sup>[12]</sup> A<sub>1c</sub> reflects longer-term glycemic control and is less influenced by acute stress. Therefore, A<sub>1c</sub> levels may provide insight into the relation between chronic glucose control and patient outcomes. Thus, it seems that HbA<sub>1c</sub> level on admission might be a more proper reflector of chronic hyperglycemia, which would detect occult diabetes as well. HbA<sub>1c</sub> can also be used to indicate the correlation between its higher levels and increased morbidity and mortality in the critically ill patients.<sup>[13,14]</sup> Yet, there are conflicting reports on the impact of chronic hyperglycemia on the outcome of critically ill patients. Previous studies showed a relationship between HbA<sub>1c</sub> and mortality in critically ill patients.<sup>[15,16]</sup> However, Britton *et al.* in their cohort of patients with diabetes presenting with acute myocardial infarction, did not observe a J-shaped association between A<sub>1c</sub> and mortality.<sup>[17]</sup>

Hence, we hypothesized that beside ICU admission hyperglycemia, HbA<sub>1c</sub> (pre-ICU control of hyperglycemia), and also targeted blood glucose control could be considered as three important factors associated with mortality. Consequently, based on the controversies in this field, in this study, we evaluated our hypothesis with showing the relationship between HbA<sub>1c</sub>, ICU admission blood sugar, and glucose control during ICU stay with mortality in critically ill patients.

## Materials and Methods

This study was approved by the Ethics Committee of Tabriz University of Medical Sciences. Five hundred patients were enrolled in this study performed in two university-based hospitals (Shohada and Imam Reza) affiliated to Tabriz University of Medical Sciences in Tabriz, Iran, from April 2012 to February 2014.

Both ICUs were surgical type ICU. Written informed consents were obtained from the patients or their surrogates. ICU admission blood sugar and HbA<sub>1c</sub> were measured for all patients. Age, sex, history of DM, comorbidities, Acute Physiology and Chronic Health Evaluation (APACHE II) score, sequential organ failure assessment (SOFA) score, hypoglycemic episodes, type of nutrition, drug history (aspirin, corticosteroids, beta blockers, metformin, and glibenclamide), mortality, and development of acute kidney injury and liver failure were noted for all patients [Table 1]. Targeted glucose control (150 mg/dl in septic patients and 140mg/dl in other patients) was performed in all patients. All patients received intravenous insulin based on their blood glucose values. Glucose measurement was performed every 1 h with glucometers (Omron Hea-230 Glucometer). If four consecutive samples were within the normal range, the intervals for glucose measurement would be increased to every 2 h. Then, if three consecutive samples were in normal range, glucose sampling would be performed every 4 h. All patients had arterial lines for blood glucose sampling and measurement was performed by equal glucometers in two hospitals. Maximum interval for glucose sampling was 4 h. If the patient was hypoglycemic, insulin was held and DW50% in the volume of (100-BS) × 0.4 mL was infused to the patient and sampling was performed every 30 min until he/she was euglycemic. Time-weighted average of glucose concentration was calculated based on the study of Finney *et al.*<sup>[18]</sup>

## Statistical analysis

Data were presented as percent and mean ± standard deviation. The primary outcome of the study was mortality. Analysis was performed with SPSS version 16. A two-sided  $P = 0.05$  was considered to be statistically significant. We used student *t*-test for comparison of mean changes between two parameters and ANOVA for comparison of changes between groups in quantitative variables. Chi-square was used for the analysis of

**Table 1: Patients' characteristics during ICU stay**

Characteristic	Survivors	Non-survivors	P value
No of patients	454 (90.8%)	46 (9.2%)	
Male	274 (60.35%)	26 (56.52%)	0.613
Age (Y)	55.1	68.28	<0.001
APACHE score	19.83	29.35	<0.001
SOFA	9.29	14.2	<0.001
Hemoglobin (g/dl)	12.2	11.7	0.017
Blood sugar (mg/dl)	132.63	157.52	<0.001
Acute kidney injury	41 (9%)	19 (41.3%)	<0.001
Hypoglycemia	35 (7.7%)	15 (32.6%)	<0.001
Diabetes mellitus	75 (19.5%)	19 (41.3%)	<0.001
Respiratory failure	2 (0.4%)	2 (4.3%)	0.005
Liver failure	3 (0.7%)	3 (6.5%)	0.001
HbA <sub>1c</sub>	6.059	7.250	<0.001

qualitative variables between groups. We analyzed the effects of ICU admission glucose, HbA<sub>1c</sub>, and hypoglycemic episode as independent variables on mortality with logistic regression analysis model.

## Results

Five hundred patients were enrolled in this study. The demographic characteristics of the patients have been presented in Table 1. The most common reasons for ICU admission were multiple trauma, brain malignancy, and disc herniation. The most common comorbidity was DM (18.8%). There was previous history of taking aspirin, corticosteroids, or beta blockers in 242 patients (48.4%). In 18.8% of patients, a history of oral glucose control agents was noted. Ninety-eight percent of patients received metabolic support as enteral nutrition, and the rest received parenteral nutrition. ICU mortality was 9.2%, and hypoglycemic episodes were reported in 10% of patients. The mean score for APACHE was  $20.7 \pm 5.8$  and mean SOFA score was  $9.7 \pm 2.7$ . We compared variables in two groups: Survivors and nonsurvivors. Nonsurvivors had significantly higher HbA<sub>1c</sub> values compared to survivors, without considering the history of diabetes ( $7.25 \pm 1.87$  vs.  $6.05 \pm 1.22$ , respectively,  $P < 0.001$ ). An almost weak correlation was observed between HbA<sub>1c</sub> and ICU admission glucose levels ( $P < 0.001$ ,  $r: 0.45$ ). ICU admission blood glucose showed a significant correlation with the risk of death ( $P < 0.001$ , confidence interval [CI]: 1.004–1.02, relative risk [RR]: 1.01). Hypoglycemic event increased the risk of death by 20%; however, this relation was not statistically significant ( $P: 0.221$ , CI: 0.927–1.58, RR: 1.2). Logistic regression analysis showed that HbA<sub>1c</sub> increased the risk of death; with each increase in HbA<sub>1c</sub> level, the risk of death doubled. However, this relation was not statistically significant ( $P: 0.161$ , CI: 0.933–1.58, RR: 1.2).

## Discussion

The concept of harmful glucose levels bears two ends: One end is being too high while the other is being too low. Our study showed that ICU admission blood glucose levels (acute hyperglycemia) and HbA<sub>1c</sub> (preexistent hyperglycemia) were correlated with patients mortality. These findings showed that acute hyperglycemia has a correlation with mortality, which might be influenced by previous hyperglycemia. Although HbA<sub>1c</sub> values have been widely investigated as an index of long-term blood glucose control and outcome predictors in diabetic patients, their predictive value in the critically ill patients admitted to ICU has received little attention.

Egi *et al.* showed that the higher mean glucose levels ( $>180$  mg/dl) during ICU stay is related to lower hospital mortality in patients with higher HbA<sub>1c</sub> ( $>7\%$ ) compared to low HbA<sub>1c</sub> ( $<7\%$ ). Zhang *et al.*<sup>[19]</sup> showed that HbA<sub>1c</sub> should be assessed only in patients without the history of DM to determine whether they suffer from hyperglycemia. A study by Plummer *et al.*<sup>[20]</sup> in critically ill patients showed that acute hyperglycemia is associated with increased mortality in patients with adequate previous glycemic control, but not in patients with abnormal pre-morbid hyperglycemia. After adjusting for age, body mass index (BMI), APACHE II, and admission type, the predicted mortality curves were no longer significant for patients with HbA<sub>1c</sub>  $<6\%$  and between  $6\%$  and  $7\%$ , probably reflecting the dominant association between APACHE II and mortality. Unfortunately, they did not assess the hypoglycemic events and only used peak blood glucose during first 48 h after ICU admission. There are numerous studies suggesting strong associations between hyperglycemia and mortality in critically ill patients, but patients with unrecognized diabetes have not been identified in these studies;<sup>[11,21–25]</sup> placing them as “not having diabetes” which is also the limitation of our study. Zaghla *et al.* showed that elevated admission glucose level is a strong predictor of short-term adverse outcome in patients with acute coronary syndrome; however, the prognostic value of HbA<sub>1c</sub> levels in these patients is still undefined.<sup>[26]</sup> The results of ADVANC study showed that a less marked reduction in HbA<sub>1c</sub> levels (i.e., from  $7.5\%$  to  $6.5\%$ ) was associated with a significant reduction of major vascular events and a nonsignificant beneficial trend in mortality.<sup>[27]</sup> On the other hand, the Action to Control Cardiovascular Risk in Diabetes study showed that a higher baseline level of HbA<sub>1c</sub> and greater reduction in its levels appeared to be associated with increased risk in the ambulatory setting, similar to the acute setting.<sup>[28]</sup> A study by Farrugia *et al.* suggests that HbA<sub>1c</sub> may not be a proper predictor of outcome in the general ICU population but may be of predictive value in diabetic ICU Patients. On the other hand, in a similar study, blood glucose levels on admission were introduced as a predictor of mortality, while no association between HbA<sub>1c</sub> and cortisol levels on admission was found.<sup>[29]</sup> A risk adjusted analysis of 120 traumatic patients by Karen *et al.* showed that patients with HbA<sub>1c</sub> of more than  $6\%$  were 4.5 times more likely to have poor outcomes compared with those with HbA<sub>1c</sub> of  $<6\%$ . However, the authors did not evaluate the impact of glucose control or acute glycemia on the outcome of patients.<sup>[30]</sup> Results of a study performed on 119 critically ill patients during the first 24 h showed that the risk of the in-hospital mortality significantly increases with HbA<sub>1c</sub> levels

above 9.3% and BMIs below 24 kg/m<sup>2</sup>; surprisingly, having no association with mortality in overweight patients, while progressively declining in those with a BMI above 35 kg/m<sup>2</sup>. The weak correlation between HbA<sub>1c</sub> and BMI suggests an independent effect of these metabolic parameters as prognostic factors in critically ill patients.<sup>[31]</sup> Kompoti *et al.* showed that a cutoff of 6.5% for HA1c could predict higher ICU mortality in patients without prior history of diabetes; but, in patients with prior history of diabetes a cutoff of 7 for HbA<sub>1c</sub> had no association with ICU mortality.<sup>[32]</sup> The possible mechanisms explaining the effects of HbA<sub>1c</sub> variability on outcomes might be as followings: Low socioeconomic status which might indicate a suboptimal management of diabetes, insulin resistance, which in itself has been implicated in the pathogenesis of diabetes complications,<sup>[33]</sup> and homeostatic imbalance; for example, through intracellular sorbitol accumulation.<sup>[34]</sup> Previous studies suggest that increased HbA<sub>1c</sub> levels are a negative prognostic marker in DM patients admitted to ICUs. The results of a cohort study in German showed that known diabetes and HbA<sub>1c</sub>-defined undiagnosed diabetes were both associated with an increased risk for all-cause mortality after 11.6 years of follow-up in this nationwide German cohort. However, adults with prediabetes, as defined by HbA<sub>1c</sub>, did not differ in their mortality risk from those with normoglycemia. A U-shaped association was found between continuous HbA<sub>1c</sub> measures and all-cause mortality, suggesting that not only high but also low HbA<sub>1c</sub> levels might be associated with an increased risk of death.<sup>[16]</sup> As DM is usually asymptomatic at early stages, many patients may not be aware of this condition on ICU admission. Acute insulin resistance is associated with worse outcomes in nondiabetic patients. In addition, critical illness characteristics influence glycemic control and clinical outcome in ICU patients. The effect of preexisting hyperglycemia in addition to acute hyperglycemia on mortality of critical ill patients might be due to the increased inflammatory cytokine concentration or relative neuroglycopenia, or perhaps other yet-unidentified mechanisms. While there has recently been a shift in focus to individualizing HbA<sub>1c</sub> targets for ambulant patients with Type 2 diabetes, the hypothesis that premorbid glycemic control may modulate the response to hyperglycemia during critical illness has not been tested.

### Limitations of study

Important limitations of this study include reliance on single glycated hemoglobin and glucose measurements at baseline and a limited number of fasting glucose measurements during the follow-up period. This study was performed in two ICUs whose most patients were surgical patients.

### Conclusion

Acute hyperglycemia secondary to critical illness-associated hyperglycemia or diabetes (both recognized and unrecognized) frequently occurs in critically ill patients and appears to have a complex relationship with mortality. Our results showed that acute hyperglycemia has a significant effect on mortality of critically ill patients, and this relation is influenced by chronic hyperglycemia.

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### Conflicts of interest

There are no conflicts of interest.

### References

1. Li L, Messina JL. Acute insulin resistance following injury. *Trends Endocrinol Metab* 2009;20:429-35.
2. Thorell A, Nygren J, Ljungqvist O. Insulin resistance: A marker of surgical stress. *Curr Opin Clin Nutr Metab Care* 1999;2:69-78.
3. Negargar S, Mahmoodpoor A, Taheri R, Sanaie S. The relationship between cerebral oxygen saturation changes and post operative neurologic complications in patients undergoing cardiac surgery. *Pak J Med Sci* 2007;23:380-5.
4. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, *et al.* Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2008. *Intensive Care Med* 2008;34:17-60.
5. Collier B, Diaz J Jr, Forbes R, Morris J Jr, May A, Guy J, *et al.* The impact of a normoglycemic management protocol on clinical outcomes in the trauma intensive care unit. *JPEN J Parenter Enteral Nutr* 2005;29:353-8.
6. Krinsley JS. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. *Mayo Clin Proc* 2004;79:992-1000.
7. Parish M, Mahmoodpoor A, Sanaie S. Validity of fasting blood sugar on the day of surgery compared with the preinduction blood glucose level in type II diabetic patients. *Pak J Med Sci* 2007;23:202-5.
8. Mahmoodpoor A, Ali-Asgharzadeh A, Parish M, Amir-Aslanzadeh Z, Abedini N. A comparative study of efficacy of intensive insulin therapy versus conventional method on mortality and morbidity of critically ill patients. *Pak J Med Sci* 2011;27:496-9.
9. Sato H, Carvalho G, Sato T, Lattermann R, Matsukawa T, Schrieker T. The association of preoperative glycemic control, intraoperative insulin sensitivity, and outcomes after cardiac surgery. *J Clin Endocrinol Metab* 2010;95:4338-44.
10. Falciglia M, Freyberg RW, Almenoff PL, D'Alessio DA, Render ML. Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. *Crit Care Med* 2009;37:3001-9.
11. Krinsley JS. Glycemic control, diabetic status, and mortality in a heterogeneous population of critically ill patients before and during the era of intensive glycemic management: Six and one-half years experience at a university-affiliated community hospital. *Semin Thorac Cardiovasc Surg* 2006;18:317-25.
12. Egi M, Bellomo R, Stachowski E, French CJ, Hart GK, Taori G, *et al.* The interaction of chronic and acute glycaemia with mortality in critically ill patients with diabetes. *Crit Care Med* 2011;39:105-11.
13. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2011;34 Suppl 1:S62-9.
14. Gornik I, Gornik O, Gasparovic V. HbA<sub>1c</sub> is outcome predictor in diabetic patients with sepsis. *Diabetes Res Clin Pract* 2007;77:120-5.
15. Takao T, Matsuyama Y, Yanagisawa H, Kikuchi M, Kawazu S.

- Association between HbA1c variability and mortality in patients with type 2 diabetes. *J Diabetes Complications* 2014;28:494-9.
16. Paprott R, Schaffrath Rosario A, Busch MA, Du Y, Thiele S, Scheidt-Nave C, *et al.* Association between hemoglobin A1c and all-cause mortality: Results of the mortality follow-up of the German National Health Interview and Examination Survey 1998. *Diabetes Care* 2015;38:249-56.
  17. Britton KA, Aggarwal V, Chen AY, Alexander KP, Amsterdam E, Fraulo E, *et al.* No association between hemoglobin A1c and in-hospital mortality in patients with diabetes and acute myocardial infarction. *Am Heart J* 2011;161:657-63.e1.
  18. Finney SJ, Zekveld C, Elia A, Evans TW. Glucose control and mortality in critically ill patients. *JAMA* 2003;290:2041-7.
  19. Zhang HY, Wu CJ, Li CS. Glycated hemoglobin A1C and diabetes mellitus in critically ill patients. *World J Emerg Med* 2013;4:201-4.
  20. Plummer MP, Bellomo R, Cousins CE, Annink CE, Sundararajan K, Reddi BA, *et al.* Dysglycaemia in the critically ill and the interaction of chronic and acute glycaemia with mortality. *Intensive Care Med* 2014;40:973-80.
  21. Rady MY, Johnson DJ, Patel BM, Larson JS, Helmers RA. Influence of individual characteristics on outcome of glycemic control in intensive care unit patients with or without diabetes mellitus. *Mayo Clin Proc* 2005;80:1558-67.
  22. Egi M, Bellomo R, Stachowski E, French CJ, Hart GK, Hegarty C, *et al.* Blood glucose concentration and outcome of critical illness: The impact of diabetes. *Crit Care Med* 2008;36:2249-55.
  23. Krinsley JS, Egi M, Kiss A, Devendra AN, Schuetz P, Maurer PM, *et al.* Diabetic status and the relation of the three domains of glycemic control to mortality in critically ill patients: An international multicenter cohort study. *Crit Care* 2013;17:R37.
  24. Kosiborod M, Inzuechi SE, Krumholz HM, Xiao L, Jones PG, Fiske S, *et al.* Glucometrics in patients hospitalized with acute myocardial infarction: Defining the optimal outcomes-based measure of risk. *Circulation* 2008;117:1018-27.
  25. Stegenga ME, Vincent JL, Vail GM, Xie J, Haney DJ, Williams MD, *et al.* Diabetes does not alter mortality or hemostatic and inflammatory responses in patients with severe sepsis. *Crit Care Med* 2010;38:539-45.
  26. Zaghla HE, Elbadry MA, Ashour AM, Abdelfatah MM. Influence of admission blood glucose and hemoglobin A1c on outcome of acute myocardial infarction. *Egypt J Intern Med* 2014;26:21-6.
  27. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, *et al.* Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358:2560-72.
  28. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC Jr., Bigger JT, *et al.* Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;358:2545-59.
  29. Farrugia DP, Sciberras S, Sant F, Abela CJ, Adami JZ, LaFerla G. Glycosylated haemoglobin (HbA1c) and cortisol levels on admission to intensive care as predictors of outcome. *Malta Med J* 2009;21:34-9.
  30. Lionel KR, John J, Sen N. Glycated hemoglobin A: A predictor of outcome in trauma admissions to intensive care unit. *Indian J Crit Care Med* 2014;18:21-5.
  31. Viana MV, Moraes RB, Fabbrin AR, Santos MF, Torman VB, Vieira SR, *et al.* Contrasting effects of preexisting hyperglycemia and higher body size on hospital mortality in critically ill patients: A prospective cohort study. *BMC Endocr Disord* 2014;14:50.
  32. Kompoti M, Michalia M, Salma V, Diogou E, Lakoumenta A, Clouva-Molyvdas PM. Glycated hemoglobin at admission in the intensive care unit: Clinical implications and prognostic relevance. *J Crit Care* 2015;30:150-5.
  33. Groop PH, Forsblom C, Thomas MC. Mechanisms of disease: Pathway-selective insulin resistance and microvascular complications of diabetes. *Nat Clin Pract Endocrinol Metab* 2005;1:100-10.
  34. The Diabetes Control and Complications Trial Research Group. Early worsening of diabetic retinopathy in the diabetes control and complications trial. *Arch Ophthalmol* 1998;116:874-86.