

*Original article*

## The Relationship between HbA1C Levels and Clinical Outcome in Patients with Traumatic Brain Injury: A Prospective Study

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### SUMMARY

**Introduction/Aim:** Recently, hemoglobin A1c (HbA1c) has been suggested as a predictor of mortality and poor clinical outcome in patients with trauma. The aim of this study was to evaluate the relationship between HbA1c values and clinical outcome in patients with traumatic brain injury (TBI).

**Methods:** In a cross-sectional study, a total of 133 TBI patients referred to the emergency department of Imam Khomeini Hospital in Sari, Mazandaran, Iran were evaluated. After transferring the patients to the neurosurgery ward, their HbA1c, fasting blood glucose (FBG) and postprandial glucose (PPG) were measured. Also, patients' Glasgow Coma Scale (GCS) score was recorded at the time of admission, 24 hours after admission and at the time of discharge from the hospital.

**Results:** The mean of GCS score of patients at the time of admission, 24 hours after admission, and at the time of discharge were 9.02 (2.09), 10.07 (2.16), and 12.98 (1.82), respectively. The mean GCS score of patients with HbA1c < 5.7% was significantly lower than of patients with HbA1c = 5.7 - 6.5% at the time of admission ( $p < 0.05$ ). At 24 hours after admission, the mean GCS score of patients with HbA1c < 5.7% was significantly lower than in other groups ( $p < 0.05$ ). However, at the time of discharge, the mean GCS score of patients with HbA1c > 6.5% was significantly lower than in patients with HbA1c = 5.7 - 6.5% ( $p < 0.05$ ). Over time, the mean of GCS scores in all patients significantly increased ( $p < 0.001$ ).

**Conclusion:** According to the results of this study it seems that HbA1c measurements cannot provide clear information about the clinical outcome of patients with TBI.

**Keywords:** HbA1c, clinical outcome, brain trauma, head trauma, traumatic brain injury

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## INTRODUCTION

Traumatic brain injury (TBI), as a chronic health condition, is associated with high morbidity, disability, and mortality (1). Annually, more than 50 million people worldwide suffer from TBI, and half of the world's population has experienced TBI once or more in their lifetime (2). TBI may be associated with increased risk of several adverse outcomes such as long-term neurological disorders, dementia, including Alzheimer's disease (3 - 7), anxiety, and depression (8 - 10).

Although determining the prognosis of outcome after TBI is an important factor for deciding on appropriate treatment and also an indicator of quality of care, prognosis of patients with TBI is highly uncertain. Previous studies which have attempted to identify potential predictors of outcome in these patients have largely produced inconclusive results (11, 12).

Hyperglycemia has been considered as a significant predictor of outcome in patients with TBI (13 - 16). It has been previously shown that early and persistent hyperglycemia is associated with higher mortality and morbidity in patients with TBI (17 - 19). Therefore, careful control of serum glucose level can potentially improve the prognosis of TBI patients (18, 19). However, the results of a meta-analysis indicate that blood glucose control was not associated with reduced mortality in patients with TBI. Nevertheless, it was associated with reduced risk of poor neurological outcomes (20).

Hemoglobin A1c (HbA1c) is a valuable test for screening and diagnosing prediabetes and diabetes. As a reliable index of glycemic control in diabetic patients, it indicates the average level of glucose over the past 2 to 3 months and stands for a marker of diabetic microvascular complications. Recently, HbA1c level has been suggested as a predictor of mortality and poor clinical outcomes in patients with trauma (21). The result of a study showed that the mortality of non-diabetic patients with cerebral hemorrhage was higher in patients with very low and high HbA1c levels. However, diabetic patients with very low HbA1c level had higher mortality rate (22).

Although the association between stress-induced hyperglycemia and higher mortality in patients with severe TBI has been previously revealed (16), few studies have evaluated the association of long-term glycemic status, as reflected by the HbA1c level, with clinical outcomes in patients with TBI (23). Therefore, the aim of the present study was to evaluate the relationship between HbA1c levels and clinical outcome in patients with TBI.

## METHODS

**Study design and sample:** In a prospective follow-up study, a total of 133 consecutive patients with TBI, referred to the emergency department of Imam Khomeini Hospital in Sari, Mazandaran province, northern Iran, were evaluated. Data were collected from May to September 2019.

**Inclusion and exclusion criteria:** The inclusion criteria were patients with TBI, aged 16 to 70 years, and referred to the hospital in less than 12 hours of sustaining trauma. The exclusion criteria were patients' death before arriving at the hospital, Glasgow Coma Scale (GCS) = 3, penetrating brain trauma, development of severe complications such as hemothorax and hemoperitoneum, and necessity of emergency surgery.

**Data collection:** Eligible patients were examined by a neurosurgeon at the time of admission to the emergency department. After transferring the patients to the neurosurgery ward, their GCS score, HbA1c, fasting blood glucose (FBG) level and postprandial glucose (PPG) were measured. Data were recorded in a researcher-made checklist which includes demographic and clinical characteristics of patients including age, sex, job, type of accident, and GCS score (at the time of admission, 24 hours after admission and at the time of discharge from the hospital).

**Ethical consideration:** Approval of institutional Ethics Committee of Mazandaran University of Medical Sciences were obtained. Also, participants were given complete assurance of confidentiality and informed consent was obtained from the substitute decision maker or the patient.

**Statistical analysis:** Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess the normality of quantitative data. The quantitative and qualitative variables were presented by mean (standard devi-

ation; SD) and number (percentage). Data were analyzed using Pearson's correlation coefficients, one-sample t-test and Chi-square statistical tests. One-way analysis of variance (ANOVA) was used to compare the difference among and between groups according to HbA1c level. Statistical package for the social sciences (SPSS) software (version 16.0, SPSS Inc., Chicago, IL, USA) was used for data analysis. P-value less than 0.05 was considered as a significance level.

## RESULTS

Participant's characteristics: A total of 133 TBI patients were included in the present study, with a mean age of 45.08 (SD = 15.09) years. Of the eligible patients, 75.94% were male, 34.59% were freelance, and 56.39% had a rollover accident. The demographic characteristics of the patients are presented in Table 1.

**Table 1.** Demographic characteristics and clinical features of patients (n = 133)

Variables	TBI patients (n = 133)
<b>Age (y)</b>	
19 - 35	41 (30.83)
36 - 53	45 (33.83)
54 - 70	47 (35.34)
<b>Sex</b>	
Male	101 (75.94)
Female	32 (24.06)
<b>Occupation</b>	
Freelance	46 (34.59)
Retired	3 (2.26)
Unemployed	12 (9.02)
Housewife	19 (14.28)
Employee	36 (27.07)
Student	17 (12.78)
<b>Type of accident</b>	
Rollover	75 (56.39)
Pedestrian	41 (30.83)
Fall	13 (9.77)
Direct injury	4 (3.01)
<b>GCS</b>	
At the time of admission	9.02 (SD = 2.09)
24 hours after admission	10.07 (SD = 2.16)
At the time of discharge	12.98 (SD = 1.82)
<b>HbA1c</b>	
< 5.7%	68 (51.13)
5.7 - 6.5%	47 (35.34)
> 6.5%	18 (13.53)
<b>PPG</b>	174.56 (SD = 51.74)
<b>FBG</b>	114.67 (SD = 26.04)
<b>History of diabetes</b>	
Yes	39 (29.3)
No	94 (70.7)
<b>Length of hospital stay (day)</b>	8.6 (3.2)

**TBI:** Traumatic brain injury; **GCS:** Glasgow coma scale; **HbA1c:** Hemoglobin A1c. **PPG:** Post-prandial glucose; **FBG:** Fasting blood glucose; **SD:** Standard deviation  
Data are presented as number (percentage) and mean (standard deviation)

**Table 2.** GCS and HbA1c of participants (n = 133)

	HbA1c level			P-value
	< 5.7%	5.7 - 6.5%	> 6.5%	
<b>GCS score</b>				
<b>At the time of admission</b>	8.64 (SD = 2.08)	9.49 (SD = 2.07)	9.22 (SD = 1.99)	0.093
<b>24 hours after admission</b>	9.71 (SD = 2.22)	10.66 (SD = 2.10)	9.83 (SD = 1.89)	0.062
<b>At the time of discharge</b>	12.90 (SD = 1.84)	13.28 (SD = 1.81)	12.56 (SD = 1.69)	0.396

**GCS:** Glasgow coma scale; **HbA1c:** Hemoglobin A1c; **SD:** Standard deviation  
Data are presented as mean (standard deviation)  
P-value was obtained with One-way ANOVA test

Clinical features of TBI patients: As presented in Table 1, the mean (SD) of GCS score at the time of admission, after 24 hours of admission, and discharge were 9.02 (2.09), 10.07 (2.16), and 12.98 (1.82), respectively. On the other hand, the mean HbA1c, PPG, and FBG levels in the patients were 5.59% (0.75), 174.56 mg/dL (51.74), and 114.67 mg/dL (26.04), respectively. Also, 51.13% of patients with TBI had HbA1c < 5.7%.

The relationship between study variables in patients with TBI: The mean GCS score of patients at the time of admission, after 24 hours of admission, and at discharge, based on their HbA1c levels, is

presented in Table 2. Patients were classified into three groups by their HbA1c level (< 5.7%, 5.7 - 6.5% and > 6.5%). There was no statistically significant difference between GCS scores and HbA1c levels ( $p > 0.05$ ). On the other hand, the mean of GCS score in all three groups increased significantly over time ( $p < 0.001$ ). In addition, the mean HbA1c levels in male and female patients were 5.53% (SD = 0.72) and 5.77% (SD = 0.81), respectively ( $p > 0.05$ ).

The mean of the three groups of HbA1c in women differed significantly in the three-time periods ( $p < 0.001$ ) (Table 3). On the other hand, the mean GCS of patients with HbA1c < 5.7% was sig-

**Table 3.** GCS score of patients according to their sex and HbA1c level (n = 133)

HbA1c level		Sex		p-value
		Male (n = 101)	Female (n = 32)	
< 5.7%	GCS at the time of admission	8.65 (SD = 2.11)	8.82 (SD = 2.04)	0.807
	GCS 24 hours after admission	9.23 (SD = 2.31)	9.87 (SD = 2.10)	0.055
	GCS at the time of discharge	12.84 (SD = 1.95)	13.36 (SD = 1.12)	0.395
5.7 - 6.5%	GCS at the time of admission	8.97 (SD = 2.01)	10.85 (SD = 1.63)	0.004
	GCS 24 hours after admission	10.09 (SD = 1.98)	12.15 (SD = 1.68)	0.002
	GCS at the time of discharge	12.88 (SD = 1.87)	14.31 (SD = 1.18)	0.014
> 6.5%	GCS at the time of admission	9.20 (SD = 2.53)	9.25 (SD = 1.16)	0.960
	GCS 24 hours after admission	9.80 (SD = 1.81)	9.88 (SD = 2.10)	0.936
	GCS at the time of discharge	12.60 (SD = 1.71)	12.65 (SD = 1.77)	0.905

**GCS:** Glasgow coma scale; **HbA1c:** Hemoglobin A1c; **SD:** Standard deviation  
Data are presented as mean (standard deviation)  
P-value was obtained with t-test

**Table 4.** GCS and HbA1c of patients according to their age (n = 133)

Age (years)	Patients' GCS	HbA1c level			p-value
		< 5.7%	5.7 - 6.5%	> 6.5%	
< 36	At the time of admission	9.10 (SD = 2.09)	10.56 (SD = 2.01)	10.50 (SD = 3.54)	0.169
	24 hours after admission	10.00 (SD = 2.30)	12.00 (SD = 1.80)	10.00 (SD = 4.24)	0.080
	At the time of discharge	13.37 (SD = 1.65)	13.78 (SD = 1.30)	12.50 (SD = 3.54)	0.593
36 - 53	GCS at the time of admission	8.28 (SD = 1.74)	9.42 (SD = 2.09)	8.57 (SD = 2.23)	0.212
	GCS 24 hours after admission	9.06 (SD = 1.92)	10.58 (SD = 1.89)	9.14 (SD = 1.35)	0.039
	GCS at the time of discharge	12.06 (SD = 1.83)	13.68 (SD = 1.70)	12.14 (SD = 1.68)	0.017
≥ 54	GCS at the time of admission	8.26 (SD = 2.31)	9.05 (SD = 2.01)	9.44 (SD = 1.51)	0.303
	GCS 24 hours after admission	9.84 (SD = 2.32)	10.11 (SD = 2.23)	10.33 (SD = 1.80)	0.848
	GCS at the time of discharge	12.95 (SD = 1.96)	12.63 (SD = 2.01)	12.89 (SD = 1.45)	0.868

GCS: Glasgow coma scale; HbA1c: Hemoglobin A1c; SD: Standard deviation

Data are presented as mean (standard deviation)

P-value was obtained with One-way ANOVA test

**Table 5.** The relationship between GCS and HbA1c of participants (n = 133)

GCS	HbA1c	
	Pearson Correlation	P-value
At the time of admission	0.150	0.087
24 hours after admission	0.074	0.401
At the time of discharge	-0.038	0.669

GCS: Glasgow coma scale; HbA1c: Hemoglobin A1c.

P-value was obtained with Pearson Correlation Coefficient

nificantly lower than patients with HbA1c = 5.7 - 6.5%, at the time of admission ( $p < 0.05$ ). At 24 hours after admission, the mean GCS of the HbA1c < 5.7% was significantly lower than in other groups ( $p < 0.05$ ). At the time of discharge, the mean GCS of patients with HbA1c > 6.5% was significantly lower than patients with HbA1c = 5.7 - 6.5% ( $p < 0.05$ ). In all patients with different HbA1c levels, the mean GCS scores increased significantly ( $p < 0.001$ ). In the HbA1c = 5.7 - 6.5% group, the mean GCS scores of women in the three-time periods of evaluation was significantly higher than in men ( $p < 0.05$ ) (Table 3.).

The mean GCS score of patients at the time of admission, after 24 hours of admission, and on discharge, based on their age, is presented in Table 4. Patients were classified into three groups by their age: < 36 years, 36 - 53 years and > 54 years). In the age group of 36 - 53 years, there was a significant dif-

ferences between patients' GCS score at 24 hours after admission and discharge, in different HbA1c levels ( $p < 0.05$ ).

There was no statistically significant relationship between HbA1c and GCS score at the time of admission, 24 hours after admission, and at discharge ( $p > 0.05$ ) (Table 5.).

## DISCUSSION

The present study showed that there was no significant relationship between chronic hyperglycemia, assessed by HbA1c level and their clinical outcome in TBI patients. Inconsistent with the present study, the results of a study in the United States showed that in patients with intracerebral hemorrhage (ICH), either higher or lower HbA1c levels

were associated with higher in-hospital mortality rate (22). To justify this discrepancy, we can point to differences in the methodology and method used to measure the severity of brain damage. In the present study, the GCS score was used to assess the clinical outcome of TBI patients, but in that study, the National Institutes of Health Stroke Scale (NIHSS) was used. In addition, differences in sample size and participant characteristics and pathology of the injury were the possible explanations for the differences in results of other studies (22, 24, 25). Inconsistent with the results of the present study, in a study by Dandapat et al., it was shown that low HbA1c levels could be associated with poor clinical outcomes after TBI and intracerebral hemorrhage. Low levels of HbA1c may often be associated with low fibrinogen, anemia, and liver disease, which can ultimately exacerbate TBI and increase the risk of bleeding in these patients (22). Aplastic anemia, splenectomy, kidney damage, and vitamin B12 deficiency can cause a false increase in HbA1c levels (26). However, in uremic and hemodialysis patients, the lifespan of red blood cells and subsequently the HbA1c level can be reduced (27). The results of a systematic review showed that among patients with acute ischemic stroke, increased HbA1c levels are associated with an increased risk of 1 year mortality, poor functional outcome at 3 months, and symptomatic intracranial hemorrhage within 24 hours of admission. Also, increased HbA1c levels in patients with hemorrhagic stroke were associated with an increased risk of the poor functional outcome within the first 3 months from admission (28).

Some previous studies suggests that HbA1c is a useful marker to predict the outcomes in TBI patients (28, 29). Considering the high energy demand of the brain and limited capacity to store glycogen, fluctuations in blood glucose in patients after TBI can be associated with poor clinical outcomes in TBI patients (30). Previous studies have noted a significant effect of higher glucose levels on poor clinical outcomes in patients after TBI (31 - 34). In relation to the risk of hypoglycemia, the results of a systematic review and meta-analysis showed that a rapid or severe increase/decrease in blood glucose would not reduce mortality in TBI patients and greatly increase the risk of hypoglycemia (20). Therefore, timely and accurate detection of blood glucose fluctuations, especially its increase in patients after TBI, is very important. It has been suggested that the severity and duration of hyperglycemia should be monitored

in these patients (20). On the other hand, the use of a continuous glucose monitoring system (CGMS) in patients after TBI is very important (35).

The results of a study in China showed that the use of discontinuous measurements of blood glucose is helpful in predicting outcomes after TBI (36). Overall, the present study showed that there was no relationship between different HbA1c levels with poor clinical outcomes in patients after TBI. Inconsistent with this finding, the results of studies in the United States and China indicated the importance of hyperglycemia and hypoglycemia on poor clinical outcomes in patients after TBI (22, 23). In justifying these inconsistencies, in addition to differences in underlying mechanisms of brain trauma (23), differences in race and ethnicity may be the cause of differences in HbA1c levels (37). This study showed that in all patients with different HbA1c levels, the GCS scores of women were higher than in men, however, these differences were statistically significant in HbA1c level, between 5.7 - 6.5%. This difference may link to female steroid hormones, which can exert neuroprotective effects through the anti-inflammatory and antioxidant mechanism and influence clinical outcomes. Theoretically, this may provide a support for developing gender-specific treatment in patients with TBI (38).

This study has a few potential limitations. Given the cross-sectional nature of our study, no inferences of causality could be drawn. Confirming our findings in a carefully designed cohort study is of paramount importance. Also, long-term follow-up was not done because of the short time for data collection. Therefore, doing more well-designed studies with long duration of follow-up is warranted. Additionally, this study was conducted at a single-center in Sari, northern Iran, which may limit its generalizability. In addition, lack of evaluation of participants' underlying diseases, such as diabetes, anemia, renal failure, which may affect the level of HbA1c in patients, was another limitation of the present study.

## CONCLUSION

In conclusion, the results of this study indicated that HbA1c measurements cannot provide good information for predicting the clinical outcomes in patients with TBI. However, future prospective studies, with long-term follow-up, are needed to eval-

uate and compare clinical outcomes between TBI patients with different HbA1c levels.

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### Conflict of interest

There are no conflicts of interest.

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## Odnos između nivoa HbA1C i kliničkog ishoda kod bolesnika sa traumatskom povredom mozga: prospektivna studija

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### SAŽETAK

**Uvod/Cilj.** Nedavno je ukazano na to da je hemoglobin A1c (HbA1c) prediktor mortaliteta i lošeg kliničkog ishoda kod bolesnika sa traumom. Cilj ovog istraživanja bila je procena odnosa vrednosti HbA1c i kliničkog ishoda kod bolesnika sa traumatskom povredom mozga (TBI–eng.).

**Metode.** Studijom preseka obuhvaćeno je ukupno 133 bolesnika sa TBI, koji su upućeni na Odeljenje hitne pomoći bolnice Imam Homeini u Sariju, Mazandaran, Iran. Nakon prebacivanja bolesnika na Odeljenje neurohirurgije, merene su vrednosti HbA1c, meren je jutarnji nivo glukoze u krvi (FBG), kao i nivo glukoze nakon obroka (PPG–eng). Takođe, skor bolesnika na *Glasgow Coma Scale* (GCS–eng.) zabeležen je u trenutku prijema, 24 sata nakon prijema i pri otpustu iz bolnice.

**Rezultati.** Srednje vrednosti GCS skora bolesnika u trenutku prijema, 24 sata nakon prijema i u vreme otpusta iznosile su 9,02 (2,09), 10,07 (2,16) i 12,98 (1,82) respektivno. Prosečan GCS skor bolesnika sa HbA1c < 5,7% bio je značajno niži nego kod bolesnika sa HbA1c = 5,7 - 6,5% u vreme prijema ( $p < 0,05$ ). Dvadeset četiri sata nakon prijema, srednji GCS skor bolesnika sa HbA1c < 5,7% bio je značajno niži nego u drugim grupama ( $p < 0,05$ ). Međutim, u vreme otpusta, srednji GCS skor bolesnika sa HbA1c > 6,5% bio je značajno niži nego kod bolesnika sa HbA1c = 5,7 - 6,5% ( $p < 0,05$ ). Vremenom se srednja vrednost GCS rezultata kod svih bolesnika značajno povećala ( $p < 0,001$ ).

**Zaključak.** Prema rezultatima ove studije, čini se da merenja HbA1c ne mogu dati jasne informacije o kliničkom ishodu bolesnika sa TBI.

**Ključne reči:** HbA1c, klinički ishod, povreda mozga, povreda glave, traumatska povreda mozga