



Impact of Diabetic Hyperglycemia on Clinical Outcomes in Patients with Diabetes Mellitus Following Traumatic Brain Injury

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ABSTRACT

AIM: To identify the effect of patients with diabetes mellitus (DM) with traumatic brain injury (TBI) in Taiwan.

MATERIAL and METHODS: Data from the trauma registry in Chang Gung Memorial Hospital, Linkou, Taiwan were collected and reviewed. Several clinical characteristics and outcomes were extracted and analyzed. The trauma databank includes 3090 patient medical records, of which 475 patients were identified as having DM. Because several baseline characteristics of patients with TBI in the DM group differed from those in the non-DM group, we performed propensity score matching to eliminate confounding factors.

RESULTS: After propensity score matching, 895 patients with TBI comprised the non-DM group, and no significant differences were noted in the baseline characteristics between groups. Patients in the DM group had more craniotomies, longer hospital stays, and longer ICU stays. We also segmented the DM group into two subgroups based on survival status. Compared with the survivor group, the nonsurvivor group had a significantly higher serum glucose level. Furthermore, patients with DM were divided into four subgroups according to their serum glucose level. The in-hospital mortality rate was higher in the subgroup with glucose levels greater than 200mg/dL than in the other subgroups. A receiver-operating-characteristic analysis revealed that the ability of serum glucose level to predict in-hospital mortality was modest, with an area under the curve of 0.641 and an associated optimal cutoff of 206 mg/dl.

CONCLUSION: DM should be considered a risk factor for patients with TBI receiving neurosurgical intervention and a predictor of longer hospitalization and stay in an intensive care unit. Moreover, in patients with TBI with DM, higher admission serum glucose levels are associated with a higher in-hospital mortality rate.

KEYWORDS: Traumatic brain injury, Diabetes, Hyperglycemia, Outcome

ABBREVIATIONS: **DM:** Diabetes mellitus, **TBI:** Traumatic brain injury, **CGMH:** Chang Gung Memorial Hospital, **ER:** Emergency department, **ISS:** Injury severity score, **ROC:** Receiver operating characteristic, **CI:** Confidence interval, **ICD:** International Classification of Diseases, **GCS:** Glasgow Coma Scale, **SBP:** Systolic blood pressure, **AIT:** Abbreviated injury scale, **TRISS:** Trauma injury severity score, **ICP:** Intracranial pressure, **ICU:** Intensive care unit, **CNS:** Central nervous system, **CV:** Cardiovascular, **GI:** Gastrointestinal, **GU:** Genitourinary, **SDH:** Subdural hematoma, **ICH:** Intracerebral hemorrhage, **BBB:** Brain blood barrier, **CAD:** Coronary artery disease

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■ INTRODUCTION

Diabetes is increasingly prevalent, both globally and in East Asian countries such as Taiwan (14,24). Diabetes mellitus (DM) is characterized by prolonged high blood glucose due to insufficient insulin levels or activity, resulting in microvascular disease (i.e. neuropathy or nephropathy) and/or macrovascular disease (i.e. atherosclerosis) (32). Furthermore, nervous system damage caused by DM may lead to cerebrovascular stroke, epilepsy, cognitive deficits, and depression (27). Therefore, studies have suggested that DM worsens unfavorable outcomes in patients with acute illness (25,35,37).

DM was previously identified as a risk factor for higher mortality rate in patients with moderate to severe trauma, which is defined by an Injury Severity Score (ISS) less than 9 (20). In addition, patients with trauma with DM were found to have a higher in-hospital morbidity rate, a longer period of ventilator dependence, and longer intensive care unit (ICU) stays (2). However, information remains scarce on the effect of DM on outcomes after isolated traumatic brain injury (TBI). Such information is critical because the negative effect of DM on bodily tissues may complicate how patients respond to and recover from TBI. Two recent retrospective analyses of data from the National Trauma Data Bank have found that patients with TBI with DM had higher mortality and complications rates than patients without diabetes do; however, these studies have reported no differences in lengths of hospital or ICU stay (18,23). However, no study has focused on the association between hyperglycemia and TBI in the East Asian population, although East Asian individuals tend to develop type 2 DM at a lower body mass index (BMI) and have a higher risk of developing renal and cardiovascular complications (24). Taiwan has the highest diabetes prevalence among the East Asian countries, and the proportion of undiagnosed cases of diabetes in Taiwan was estimated at 52.6%, much higher than the 27% in the United States (24).

A previous study demonstrated that TBI induced hyperglycemia status and that patients with severe TBI had worse outcomes if they had higher admission serum glucose levels (16). Interestingly, a recent prospective randomized study demonstrated that patients with trauma with persistent hypoglycemia had significantly higher rates of morbidity and mortality (6). Therefore, the present study focused on the effect of hyperglycemia on outcomes in patients with TBI with DM. We aimed to evaluate the effect of DM on the mortality, complications, and rate of craniotomy in patients with TBI, with a specific focus on the effect of admission blood glucose level on mortality in DM compared with patients without DM.

■ MATERIAL and METHODS

Data Source

This study was a retrospective review of data collected from the trauma registry at Chang Gung Memorial Hospital (CGMH), Linkou, Taiwan (19). Approval was obtained from the Chang Gung Memorial Hospital Institutional Review Board before the study was conducted. We reviewed the registry data collected

from 2015 to 2017 and identified 3,090 medical records for patients with TBI. Patients with TBI were identified using the International Classification of Diseases, Ninth Revision (ICD-9) codes 310.2, 348.1, 348.5, 738.10, 803.xx, 850.xx–853.xx, and 959.01, and Tenth Revision (ICD-10) codes S00–S09. Trauma and with DM were identified using the ICD-9 code 250.xx and ICD-10 codes E10.xx and E11.xx.

Covariates and Outcomes

The following data were collected and analyzed: age, gender, Glasgow Coma Scale score (GCS) at triage, systolic blood pressure (SBP) at triage, Abbreviated Injury Scale (AIS) for the head, ISS, and Trauma Injury Severity Score (TRISS). The type of operations the patients with TBI received (intracranial pressure [ICP] monitor placement, craniotomy, and craniectomy) and the ICU and hospital length of stay were also recorded. Any complications that occurred during hospitalization, including central nervous system (CNS), cardiovascular (CV), respiratory, gastrointestinal (GI), genitourinary (GU), orthopaedic, hematological, and infection-related complications, were recorded. Patients with TBI were divided into five groups based on discharge disposition: 1) recovery, 2) transfer to a nursing home, 3) transfer to a rehabilitation unit, 4) transfer to a local hospital, and 5) death. We also recorded the admission serum glucose level to determine the patients' hypo or hyperglycemia status.

Patients that died in the emergency department before being transferred to another facility were excluded. The primary outcome measure was mortality. Secondary outcomes were hospital and ICU length of stay, discharge disposition, and the number of patients receiving craniotomy.

Statistical Analysis

An initial comparison of all clinical characteristics and the aforementioned outcome measures indicated that some baseline values differed significantly between patients with and without DM. To minimize the effects of confounding factors on our results, we used propensity score matching for several items, including age, gender, shock status in the Emergency Department, and ISS. Propensity score matching was conducted to reduce the effect of possible confounders when comparing the outcomes between the DM and non-DM groups. The propensity score estimated indicated the probability of changes in outcomes in the DM group based on the values of covariates using multivariate logistic regression. The variables selected to calculate the propensity score were age, gender, hypotension at admission (SBP < 90 mmHg), and admission scores for ISS and GCS. Each patient in the DM group was matched with two patients in the non-DM group using a greedy nearest neighbor algorithm with a caliper that was 0.2 times the standard deviation of the logit of the propensity score, with random matching order and without replacement.

The demographics characteristics, clinical characteristics, complications, and outcomes between the DM and non-DM groups were compared using Fisher's exact test for categorical variables and an independent sample *t* test for continuous variables. To evaluate the ability of admission

glucose level to predict in-hospital mortality in patients with diabetes, a receiver operating characteristic (ROC) curve analysis was conducted. Statistical significance was indicated by a two-tailed p value <0.05. No multiple testing (multiplicity) adjustments were applied in this study. Data analyses were conducted using SPSS 25 (IBM SPSS Inc, Chicago, Illinois).

RESULTS

Demographic and Clinical Characteristics

During the 3-year study period from 2015 to 2017, a total of 3,090 patients with TBI were included. Among this cohort, 475 patients (15.4%) were identified as having DM. Compared with the non-DM group, patients in the DM group were predominantly female, older, and less likely to experience shock and had higher AIS-head scores, higher ISS scores,

and lower TRISS scores (Table I, left panel). Furthermore, compared with those in the non-DM group, more patients with TBI in the DM group had subdural hematoma (SDH) and intracerebral hemorrhage (ICH) and fewer patients had skull fractures. Surgical intervention in patients with TBI with DM was more likely to involve ICP monitors and craniotomies than that in patients with TBI without DM (Table I, left panel).

Because of large discrepancies between many factors, such as the number of patients, gender, and age, propensity score matching was conducted between the patients with TBI with and without DM. A total of 475 patients with TBI in the DM group were matched with 895 patients with TBI in the non-DM group: 420 patients with DM were matched with two patients without DM, and 55 patients with DM were matched with one patient without DM (Table I, right panel). No significant differences in demographic characteristics, traumatic severity,

Table I: Demographics and Clinical Characteristics of TBI Patients with DM and Non-DM Groups Before (Left Panel) and After (Right Panel) Propensity Score Matching

Variable	Data before matching			Data after matching		
	DM (n = 475)	Non-DM (n = 2,615)	p	DM (n = 475)	Non-DM (n = 895)	p
Demographics						
Female	179 (37.7)	851 (32.5)	0.030	179 (37.7)	341 (38.1)	0.907
Age (years)	69.1 ± 12.8	44.5 ± 23.8	<0.001	69.1 ± 12.8	68.4 ± 13.4	0.387
Traumatic severity						
Shock (SBP <90 mmHg)	5 (1.1)	102 (3.9)	0.001	5 (1.1)	11 (1.2)	1.000
GCS level	12.4 ± 4.0	12.5 ± 3.9	0.483	12.4 ± 4.0	12.5 ± 3.9	0.408
GCS group			0.413			0.676
3-8	98 (20.6)	528 (20.2)		98 (20.6)	172 (19.2)	
9-13	67 (14.1)	316 (12.1)		67 (14.1)	118 (13.2)	
14-15	310 (65.3)	1,771 (67.7)		310 (65.3)	605 (67.6)	
AIS-head	3.8 ± 1.3	3.3 ± 1.6	<0.001	3.8 ± 1.3	3.7 ± 1.3	0.312
ISS score	19.9 ± 8.4	18.7 ± 9.7	0.012	19.9 ± 8.4	19.7 ± 8.2	0.759
NISS score	21.9 ± 9.9	21.5 ± 10.6	0.387	21.9 ± 9.9	21.9 ± 9.2	0.892
TRISS score	0.83 ± 0.20	0.89 ± 0.18	<0.001	0.83 ± 0.20	0.85 ± 0.20	0.331
Type of brain Insult						
Skull fracture	115 (24.2)	806 (30.8)	0.004	94 (19.8)	213 (23.8)	0.102
EDH	118 (24.8)	721 (27.6)	0.239	105 (22.1)	212 (23.7)	0.545
SDH	290 (61.1)	1,305 (49.9)	<0.001	296 (62.3)	543 (60.7)	0.561
SAH	261 (54.9)	1,317 (50.4)	0.072	265 (55.8)	488 (54.5)	0.690
ICH	142 (29.9)	635 (24.3)	0.011	151 (31.8)	277 (30.9)	0.760

DM: Diabetes mellitus, **GCS:** Glasgow Coma Scale, **SBP:** Systolic blood pressure, **AIS:** Abbreviated injury scale, **ISS:** Injury severity score, **NISS:** New injury severity score, **TRISS:** Trauma injury severity score, **EDH:** Epidural hematoma, **SDH:** Subdural hematoma, **SAH:** Subarachnoid hemorrhage, **ICH:** Intracranial hemorrhage.

Values are given as frequency (percentage) for categorical variable or mean ± standard deviation for continuous variable.

or type of brain injury were observed between the DM and non-DM groups after matching (Table II, right panel).

Complications and Outcomes

Before propensity score matching, the two groups did not significantly differ with respect to complications related to infection or to the central nervous, cardiovascular, gastrointestinal, respiratory, and hematological systems (Table II, left panel). However, compared with patients without DM, patients with DM had significantly more genitourinary complications (Table II, left panel). The prematched groups

also significantly differed with respect to in-hospital outcomes; compared with the non-DM group, the DM group had a significantly longer ICU length of stay, received more craniotomies, had poorer discharge disposition, and had a higher in-hospital mortality rate (Table II, left panel).

After propensity score matching, the DM and non-DM groups did not significantly differ with respect to complications, including genitourinary complications (Table II, right panel). Interestingly, the number of craniotomies was significantly greater in the DM group than in the non-DM group ($p=0.040$). The DM group had a significantly longer ICU length of stay

Table II: Complications and in Hospital Outcomes of TBI Patients in the DM and non-DM Groups Before (Left Panel) and After (Right Panel) Propensity Score Matching

Variable	Data before matching			Data after matching		
	DM (n=475)	Non-DM (n=2615)	P	DM (n=475)	Non-DM (n=895)	P
Complication						
CNS	23 (4.8)	107 (4.1)	0.456	89 (18.7)	172 (19.2)	0.885
CV	3 (0.6)	14 (0.5)	0.737	3 (0.6)	4 (0.4)	0.699
Respiratory	135 (28.4)	655 (25.0)	0.123	135 (28.4)	233 (26.0)	0.370
GI	8 (1.7)	24 (0.9)	0.138	8 (1.7)	8 (0.9)	0.198
GU	36 (7.6)	123 (4.7)	0.013	36 (7.6)	74 (8.3)	0.678
Hematology	7 (1.5)	22 (0.8)	0.194	7 (1.5)	12 (1.3)	0.813
Infection	12 (2.5)	49 (1.9)	0.368	12 (2.5)	19 (2.1)	0.703
In-hospital outcome						
LOH (day)	12.6 ± 14.2	11.7 ± 61.7	0.731	12.6 ± 14.2	10.9 ± 13.1	0.024
ICU LOS (day)	2.7 ± 5.8	2.1 ± 4.9	0.014	4.1 ± 7.5	3.0 ± 4.8	0.001
ICP monitor	40 (8.4)	149 (5.7)	0.028	41 (8.6)	59 (6.6)	0.190
Craniotomy	83 (17.5)	310 (11.9)	0.001	63 (13.3)	92 (10.3)	0.107
Craniectomy	4 (0.8)	44 (1.7)	0.226	5 (1.1)	8 (0.9)	0.775
Number of craniotomy			0.002			0.040
0	392 (82.5)	2,304 (88.1)		412 (86.7)	803 (89.7)	
1	78 (16.4)	301 (11.5)		55 (11.6)	88 (9.8)	
2	5 (1.1)	10 (0.4)		8 (1.7)	4 (0.4)	
Discharge disposition			0.001			0.592
Recovery	345 (72.6)	2,120 (81.1)		345 (72.6)	682 (76.2)	
Nursing home	42 (8.8)	151 (5.8)		36 (7.6)	57 (6.4)	
Rehabilitation	18 (3.8)	88 (3.4)		24 (5.1)	44 (4.9)	
Transfer to local hospital	5 (1.1)	20 (0.8)		5 (1.1)	6 (0.7)	
In-hospital death	65 (13.7)	236 (9.0)	0.002	65 (13.7)	106 (11.8)	0.345

DM: Diabetes mellitus, **CNS:** Central nervous system, **CV:** Cardiovascular, **GI:** Gastrointestinal, **GU:** Genitourinary, **ICU:** Intensive care unit, **ICP:** Intracranial Pressure, **LOH:** Length of hospitalization, **LOS:** Length of staying
Values are given as number (%) or mean ± standard deviation.

(4.1 vs. 3.0 days; $p=0.001$; Figure 1). Furthermore, hospital length of stay, which did not significantly differ between the prematched groups, was significantly longer in the DM group than in the non-DM group after matching (12.6 vs. 10.9 days; $p=0.024$).

Glucose Level and in-Hospital Death in Patients with Diabetes

To understand the effect of hyperglycemia on patients with TBI with DM, the group was subdivided into two groups according to the survival status upon discharge. The results indicated that serum glucose level upon arrival in the ER was significantly greater in the nonsurvivor group than in the survivor group (247.3 vs. 203.9 mg/dl, $p<0.001$; Figure

2A). In another analysis, the patients with TBI with DM were subdivided into four groups according to their serum glucose levels. The serum glucose levels of patients in groups 1, 2, 3, and 4 were <120 , 121–160, 161–200, and >200 mg/dl, respectively. Notably, in-hospital mortality rate was not dependent on glucose concentration, but mortality rate significantly differed when glucose concentration > 200 mg/dl (19.4%; Figure 2B).

An ROC analysis indicated that serum glucose level could predict in-hospital mortality, with an area under the curve of 0.641 (95% confidence interval [CI]: 0.563–0.719, $p=0.0004$). The associated optimal cutoff was 206 mg/dl with a sensitivity of 65.6% (95% CI: 52.3%–77.3%) and a specificity of 59.2% (95% CI: 54.1%–64.2%; Figure 3).

DISCUSSION

DM is a metabolic disease closely linked to multiple systemic diseases and is a major global health problem in our modern era (28). Multiple studies have indicated that DM may increase in-hospital morbidity in patients with trauma, as demonstrated by outcomes such as longer ICU stays and longer periods of ventilator support (2,4,11). However, few studies have demonstrated an association between DM and higher mortality rates in patients with TBI (18,23). Furthermore, prior to the present study, no study had focused on the East Asian population, which comprises 21.7% of the world population. East Asians, especially people in Taiwan, tend to develop type 2 diabetes at a lower mean BMI and have a higher risk of developing renal and cardiovascular complications relative to people of European descent (24). Therefore, research into the effects of DM on outcomes in patients with TM is imperative. In our study of Taiwanese patients for the 2015–2017 period, patients with TBI with DM had a significantly higher mortality rate and less favorable discharge disposition than did patients with TBI without DM before propensity score matching.

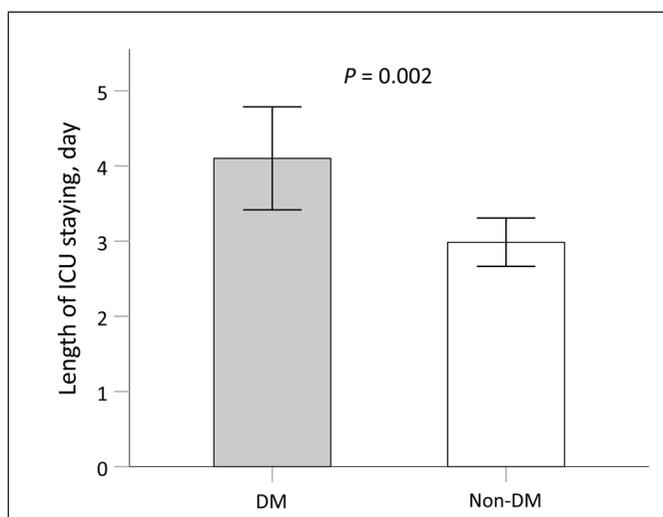


Figure 1: Length of ICU stays for patients with TBI with and without DM. Continuous data are presented in terms of the mean and 95% confidence interval.

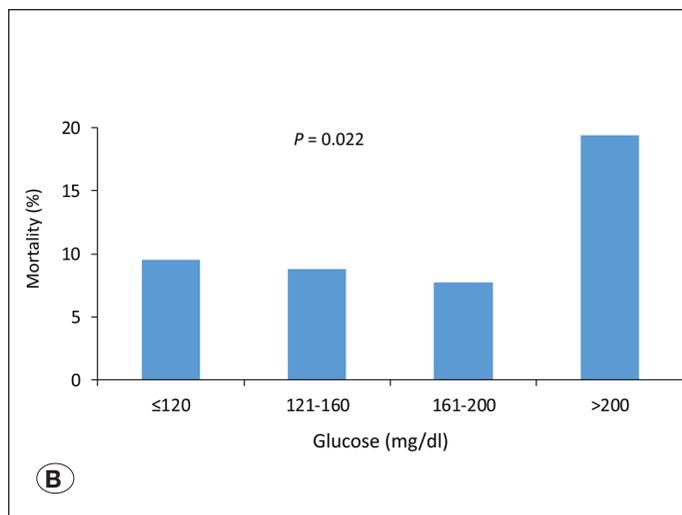
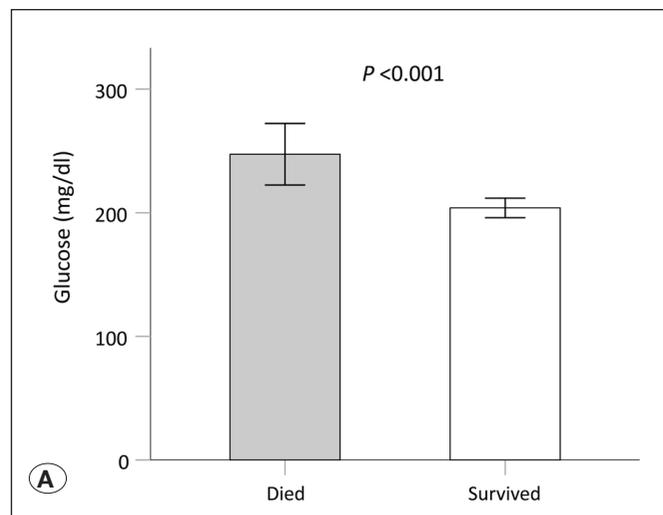


Figure 2: Serum glucose levels in patients with TBI with DM. **A)** Glucose levels of patients with TBI with DM that died or survived the admission; **B)** in-hospital mortality rate of patients with TBI with DM, stratified by serum glucose level. Continuous data are presented in terms of the mean and 95% confidence interval.

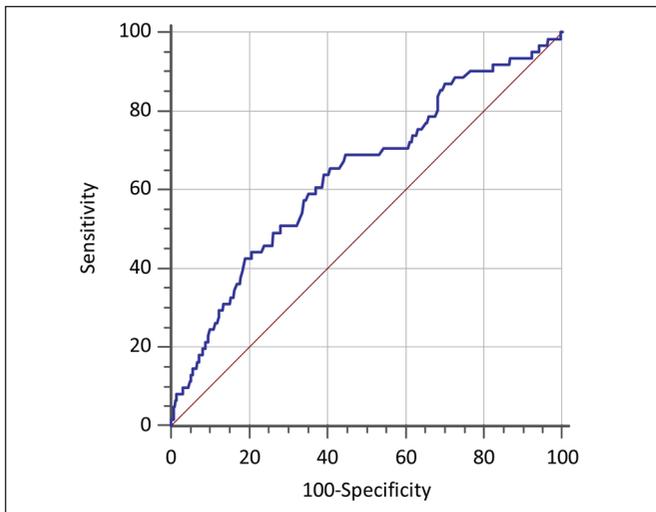


Figure 3: Receiver operating characteristic curves of serum glucose level in discriminating in-hospital mortality. The area under the curve was 0.641 (95% confidence interval: 0.563–0.719; $p=0.0004$). The associated optimal cutoff was 206 mg/dl with a sensitivity of 65.6% (95% CI: 52.3%–77.3%) and a specificity of 59.2% (95% CI: 54.1%–64.2%).

However, we observed significant differences in several demographic and clinical characteristics (e.g., age and gender) between the DM group and the non-DM group, resulting in a false positive result. After propensity score matching, several of the significant differences in demographics and clinical characteristics disappeared, suggesting that their occurrence in patients with TBI with DM was likely related to medical comorbidities. A previous study examined patients with TBI with DM in the United States (23). These patients had several baseline characteristics similar to patients in our study (age, number of patients with GCS score ≤ 8 , and shock), but patients in our study had lower mortality, higher ISS scores, and were more likely to have GCS scores between 9 and 12. In our study, patients with TBI with DM had a longer ICU and hospital length of stay relative to patients with TBI without DM. A variety of negative diabetes-related physiological outcomes have been documented in patients with diabetes and in experimental animal models (12,32). One study demonstrates that hyperglycemia can impair the immune system by altering the innate immune system (12). Unsurprisingly, patients with brain injuries are at greater risk of developing pneumonia, which increases the duration of ventilator dependence and the risk of other infections upon admission (2). DM can also cause microvascular injury, which can damage the kidneys and increase the risk of acute kidney injury during hospitalization (2). These findings jointly imply that TBI in patients with DM can lead to a longer ICU and hospital length of stay.

Our data revealed that patients with TBI with DM received craniotomies at a significantly higher rate than did patients with TBI without DM. Craniotomy is a life-saving surgical intervention for treating conditions such as hematoma expansion or brain parenchyma edema. Rau et al. observed a higher serum glucose level in patients with DM following a traumatic event (30). Interestingly, patients with diabetes

with hyperglycemia tend to have greater hematoma volume and expansion (8,15). This phenomenon is potentially related to microvascular changes in the brain in patients with diabetes (26). Increasing evidence has indicated that DM may lead to changes in histological and vascular pathology, including collagen degradation, capillary basal membrane swelling, endothelial degeneration, and the accumulation of lipid peroxidation byproduct in the cerebral vessels (26,28). These abnormal changes can result in greater vulnerability to brain injury. Increased cerebral hematoma volume, which is ameliorated by plasma kallikrein, was observed in diabetic animals with hyperglycemia compared with non-diabetic controls (22). Another factor for consideration is blood–brain barrier dysfunction following TBI. Edematous change is the leading cause of mortality in patients with TBI (36). Furthermore, experimental studies have demonstrated that DM upregulates the permeability of the blood–brain barrier by compromising its integrity (1,10,28). Altered glycemic conditions, such as those observed in patients with diabetes, are prodromal to BBB impairment (31,33). Therefore, the effect caused by brain edema could be more severe in patients with TBI with DM (23).

The brain is the most complicated and energy-consuming organ in the human body (9,29). Therefore, glucose homeostasis is tightly maintained by several physiologic responses, including potent neuroendocrine regulatory mechanisms (7,9). For patients with TBI, evidence has indicated that a high serum glucose level and presence of hyperglycemia during the first 24 hours after admission are independent risk factors for unfavorable outcomes and a higher mortality rate (38,13,16,17,21,23). However, the mechanisms underlying the detrimental effects of stress-induced hyperglycemia and those underlying DM-related hyperglycemia may differ. Stress-induced hyperglycemia is an acute process induced by a surge of stress hormones and a surge in cytokine production (29). By contrast, DM-related hyperglycemia is a chronic process linked to several microvascular disorders, such as coronary artery disease (CAD), peripheral vascular disease, and nephropathy (3). Few studies have focused on the impact of hyperglycemia in patients with DM following TBI. In this study, we demonstrate that, in an East Asian population, mortality is associated with hyperglycemia in patients with DM with TBI, especially for patients with admission serum glucose levels higher than 206 mg/dl. This phenomenon may be related to two mechanisms. First, traumatic injury to the brain may increase sympathetic activity, which subsequently increases systemic serum epinephrine level; this effect is inversely correlated with GCS score (5). In addition, increased blood epinephrine levels can increase serum glucose levels. A low GCS score, which is a predictor of poor outcomes, has been associated with higher serum epinephrine and glucose levels (5). Notably, high serum epinephrine can induce adverse effects on the CNS by aggravating trauma-related nervous system ischemia (5,39). Second, TBI can induce ischemic changes and peri-infarct depolarizations (34,39). Glucose is a major aerobic and anaerobic energy source for the brain (39). High serum glucose levels during incomplete brain ischemia can lead to continuous anaerobic glycolysis and lactate accumulation (39). Lactate accumulation creates

an environment that encourages tissue acidosis, which subsequently triggers an influx of calcium ions to the brain cells and the lipolytic release of intracellular cytotoxic free fatty acids (39). This process eventually induces cell death. Therefore, high admission serum glucose level could be both a cause and consequence of severe brain injury.

Limitation

This was a retrospective analysis of data collected from a single institution. Although the participants were matched for sex, age, ISS, and shock status upon admission, some unidentified factors could have affected the outcome of patients with TBI. Patients with type 1 or type 2 DM could not be differentiated in our database, although these two types of DM differ in their pathophysiology. Because we collected data from an existing database, we could not obtain data on several DM-related clinical characteristics that can affect clinical outcomes, including glycohemoglobin level, the status of insulin dependence, and DM disease duration for each patient.

Compared with patients without DM, those with DM are more likely to have comorbidities, such as cardiopulmonary disease, hypertension, cerebrovascular disease, and renal disease, compared with patients without DM, thus making this group more vulnerable. Therefore, studies that control for these comorbidities may help clarify the increase in morbidity and mortality in patients with TBI with DM.

CONCLUSION

DM is a significant risk factor for patients with TBI receiving neurosurgical interventions and is considered a predictor of longer ICU and hospital length of stay. Our study on an East Asian population suggests that higher admission glucose levels in patients with TBI with DM are associated with a higher mortality rate. Further research is needed to determine if different treatment protocols should be considered for patients with TBI with and without DM. Moreover, further studies are warranted to evaluate whether the aggressive control of serum glucose levels can improve the clinical outcomes of TBI patients with DM.

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AUTHORSHIP CONTRIBUTION

Study conception and design: ZHL, CCT
 Data collection: CCT, TWC, CCL
 Analysis and interpretation of results: CCT, PKY, CCC, PHT
 Draft manuscript preparation: CCT, YCH
 Critical revision of the article: ZHL, NYC, PKY
 Other (study supervision, fundings, materials, etc...): ZHL, YCH, CCC
 All authors (CCT, YCH, PHT, PKY, TWC, CCL, CCC, NYC, ZHL) reviewed the results and approved the final version of the manuscript.

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