Patterns and Effects of Admission Hyperglycemia And Inflammatory Response in Trauma Patients: A Prospective Study

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Abstract

Background: Hyperglycemia following trauma could be a response to stress. The constellation of the initial hyperglycemia, proinflammatory cytokines and severity of injury among trauma patients is understudied. We aimed to evaluate the patterns and effects of on-admission hyperglycemia and inflammatory response in a level 1 trauma center admissions.

Methods: A prospective, observational study was conducted for adult trauma patients who were admitted and tested for on-admission blood glucose, hemoglobin A1c, interleukin (IL)-6 ,Il-18 and hs-CRP. Patients were categorized into 4 groups (non-diabetic normoglycemic, diabetic normoglycemic, diabetic hyperglycemic (DH) and stress-induced hyperglycemic (SIH)). The inflammatory markers were measured on 3 time points (admission, 24 h, and 48 h). Pearson's correlation test and logistic regression analysis were performed. We hypothesized that higher initial readings of blood glucose and cytokines are associated with severe injuries and worse in-hospital outcomes in trauma patients.

Results: During the study period, 250 adult trauma patients were enrolled. Almost 13% of patients presented with hyperglycemia (SIH&DH); of whom 50% had SIH. Compared to the other 3 groups; SIH patients were younger, had significantly higher ISS, higher IL-6 readings, prolonged hospital length of stay and higher mortality. The SIH group had lower Revised Trauma Score (p=0.005), lower Trauma Injury Severity Score (p=0.01) and lower GCS (p=0.001). IL-18 and hs-CRP were comparable among the study groups. Compared to the normoglycemia groups, patients with hyperglycemia had elevated high-sensitive troponin T (p=0.001) and required more blood transfusion (p=0.03). Patients with hyperglycemia had 3-times higher in-hospital mortality than the normoglycemia groups (p=0.02). A significant correlation was identified between initial blood glucose and serum lactate, IL-6, ISS and hospital length of stay. IL-6 correlated well with ISS (r=0.40, p=0.001). On- admission blood glucose had age-sex-GCS adjusted odd ratio 1.20(95% CI 1.06-1.33, p=0.003) for severe injury (ISS≥16).

Conclusions: On-admission hyperglycemia is associated with a significant severer injury than normoglycemia patients. Initial blood glucose correlates with serum IL-6 which indicates a potential role of the systemic inflammatory response in the disease pathogenesis among the injured patients. On-admission glucose level could be a useful marker of injury severity, triage and risk assessment in trauma patients.

This study was registered at the ClinicalTrials.gov (Identifier: NCT02999386), retrospectively Registered on December 21, 2016 https://clinicaltrials.gov/ct2/show/NCT02999386.

Introduction

Hyperglycemia following trauma is a hypermetabolic response to stress which can be associated with a significant morbidity and mortality [1]. Some investigators have suggested that admission glucose levels reflect the physiological stress reaction to injury and or severe bleeding and thus could be used as a potential predictor of outcomes [2–4].

The trauma-related metabolic surge and associated stress-induced hyperglycemia (SIH) were found to correlate with serum cortisol and catecholamine levels [5]. It has been suggested that insulin production is suppressed in trauma patients due to systemic stress response secondary to elevated serum glucagon, catecholamine and cytokines [6–8].

Assessment of glycosylated hemoglobin (HbA1c) level is considered as a useful tool to distinguish occult (not known before) diabetes mellitus (DM) from SIH [9]. Kopelman et al., [10] reported that 18% of trauma patients presented with hyperglycemia, of whom 22% had occult DM which represented 4% of the total screened trauma patients. The possible mechanism of the adverse effects of hyperglycemia may differ in patients with SIH as compared to DH. SIH is an acute process, initiated by the release of stress hormones and cytokines, while DH is a chronic process associated with subsequent microvascular changes [11].

Moreover, there is a relationship between hyperglycemia and altered cellular metabolism in critically ill patients that results in insulin resistance and release of systemic inflammatory mediators [6]. Earlier studies suggested that proinflammatory cytokines such as interleukin (IL)-6 and IL-18 are involved in glucose metabolism and insulin action; therefore, hypercytokinemia may have a potential role in increased glucose levels [6, 12, 13]. This indicates that immunoneuroendocrine alterations might be involved in the pathophysiology of SIH during acute illnesses [14]. As most observations on the association of cytokines with hyperglycemia are based on experimental studies, there is a need to explore such relationship with respect to the clinical outcome in trauma patients. Herein, this prospective study aims to evaluate the patterns and effects of on-admission hyperglycemia, pro-inflammatory cytokine and severity of injury in trauma patients.

We hypothesized that higher initial readings of blood glucose and cytokines are associated with severe injuries and worse in-hospital outcomes in trauma patients.

Materials And Methods

A prospective observational study was conducted for trauma patients who were admitted to level 1 trauma center at Hamad General Hospital (HGH) between October 2016 and July 2019. Inclusion criteria were adult (≥ 18 years) trauma patients (both genders) presented to the emergency department who were investigated for random blood glucose level and HbA1C within 5 hours of hospital admission. Exclusion criteria included patients declined to participate or in whom random glucose level and HbA1C were not measured on time, vulnerable populations (children, pregnant women) and alcohol consumers. All trauma patients underwent thorough clinical assessment and resuscitation according to the Advanced Trauma Life Support (ATLS) guidelines. Potential subjects were enrolled after obtaining written informed consent either by subject or his/her next-of-kin or deferred consent for blood investigations and use of data with secured confidentiality of personal information. The Institutional Review Board (IRB# 14471/14) of Hamad Medical Corporation has approved this study. This study is registered at the ClinicalTrials.gov (Identifier: *NCT02999386*).

Sample size

sample size was calculated considering the prevalence of SIH in trauma patients that ranges from 10–17% for all trauma admissions [15, 16] with a precision of estimate (margin of error) of 5% and a 95% level of confidence. Using the single proportion equation for dichotomous variables in the nMaster 2.0 sample size software package, the required sample size was 250 consecutive trauma patients.

Study variables

Data included patients' demographics, (age, gender, nationality), mechanism of injury, initial vitals (heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure and shock index), routine laboratory findings such as hemoglobin, base deficit, serum lactate, and blood glucose levels were recorded at the baseline, after 24 h and 48 h. Other investigations included white blood cell count (WBC), platelet count, high-sensitive troponin T (hs-TnT), HbA1C, and blood ethanol levels. We have collected information about history of DM, anti-diabetic medications, associated injuries, injury severity score (ISS), Glasgow Coma Score (GCS), Revised Trauma Score (RTS), Trauma Injury Severity Score (TRISS), surgical intervention, blood transfusion, hospital length of stay, intensive care unit stay, in-hospital complications (pneumonia, acute respiratory distress syndrome, renal failure, and sepsis) and hospital mortality. Shock index (SI) was defined as initial heart rate divided by the initial systolic blood pressure.

The main exposure was hyperglycemia, defined as random serum glucose 200 mg/dL (11.1 mmol/l) or more. This cutoff level of glucose was previously used to define hyperglycemia by earlier studies in trauma patients [15, 17, 18]. DM was determined by patient history and/or admission HbA1c $\geq$ 6.5%. This level of HbA1c is based on current recommendations for the diagnosis of DM from the American Diabetes Association [19]. Stress-induced hyperglycemia (SIH) was defined as hyperglycemia on admission in patients with normal HbA1c in the index admission [20].

Serum levels of CRP, IL-6 and IL-18

On admission, 5 ml blood specimen was drawn in red vacutainer for proinflammatory cytokines and hs-CRP assay after recruitment in the study followed by 5 ml blood sampling repeated after 24 and 48 h post admission. The blood specimens were allowed to clot for half an hour and then centrifuged at 4500 rpm for 5 min to separate serum which was aliquoted in duplicates and stored at -80 °C in cryovials until analysis.

Briefly, to measure the concentrations of serum hs-CRP, IL-6 and IL-18, an enzyme-linked immunosorbent assay (ELISA) was performed using commercially available kits for cytokine detection (R&D Systems. The preparation of all reagents, the working standards and protocol were followed according to the manufacturer's instructions. The absorbance was read using ELISA reader (TECAN) at 450 nm and 570 nm dual filters. The minimum detectable dose for hs-CRP was 0.005 ng/ml, for IL-6 was 0.7 pg/ml and for IL-18 was 1.25 pg/ml. All the samples were thawed only once and assayed in duplicate. In addition, we recruited 50 age-sex matched healthy volunteers as controls to identify the reference values of inflammatory markers in our community; the mean serum levels of IL-6, IL-18 and hs-CRP were 1.95, 22.9 and 3.0, respectively.

Statistical analysis

Data were reported as proportion, mean (± standard deviation), confidence intervals, median, and range, when applicable. The levels of blood glucose, serum lactate, base excess, IL-6, IL-18, hs-CRP, complications and outcome were compared based on ISS (mild, moderate & severe). Trauma patients were first compared as 2 groups based on the initial glucose levels (normoglycemic vs hyperglycemic). Then trauma patients were divided into 4 subgroups based on the initial glucose and HbA1c values (non-diabetic normoglycemic, stress-induced hyperglycemia (SIH), diabetic normoglycemic, diabetic hyperglycemic (DH)) (Fig. 1). The study groups were compared using χ^2 test for categorical variables and One-way ANOVA or Student-T test for comparison of continuous variables. A significant difference was considered when the 2-tailed p- value was less than 0.05. Moreover, the percentages of change in the mean values of IL-6, IL-18, and hs-CRP from the baseline values were expressed as mean and 95% confidence interval (95% CI). Logistic regression analysis was performed to determine the age-sex-GCS adjusted odd ratio of on-admission blood glucose for the injury severity (ISS ≥ 16) and hospital mortality. Also, correlation of the average rate of change of inflammatory markers with respect to initial glucose level, ISS, TRISS and hospital length of stay was performed using Pearson's correlation. Data analysis was carried out using the SPSS version 18 (SPSS Inc., Chicago, Illinois).

Results

Patient and Injury Characteristics

During the study period, 250 trauma patients were enrolled. Figure 1 shows the study design. The vast majority of patients were males (98.0%) with mean age of 35.1 ± 10.1 years. The mean body mass index (BMI) was 26.3 ± 11.1 kg/m^2, systolic blood pressure was 124.9 ± 20.7 mmHg, and diastolic blood pressure was 78.2 ± 13.9 mmHg. The frequently injured body region was lower extremity (45.2%) followed by chest (40.4%), head (30.0%) and upper extremities (29.6%). The average glucose level at baseline was 8.38 mmol/l (95% CI; 8.01–8.74) and HbA1c was 5.61 (5.47–5.76). The mean ISS was 14.7 ± 10.1, RTS score was 7.45 ± 1.13 and TRISS was 0.9566 ± 0.12. Blood transfusion was required in 28% cases and 3.2% developed in-hospital complications. The overall hospital mortality was 4.8% (12 patients).

Normoglycemia *vs* Hyperglycemia

In the trauma cohort (n = 250), 13% of the patients had hyperglycemia on their initial presentation, of which 50% had SIH and 50% had diabetic hyperglycemia.

Table 1 compares the demographics, clinical presentation and outcome of trauma patients according to the initial blood glucose levels (hyperglycemia versus normoglycemia). The two groups were comparable for age, gender and BMI. Compared with the normoglycemia group, hyperglycemic patients had higher HbA1c and positive hsTnT (51.6% vs. 16.2%; p = 0.001). In the hyperglycemia group, serum concentrations of IL-6 at baseline, at 24 h and 48 h post trauma were significantly higher than those of the normoglycemia group. Moreover, the hyperglycemia group had a significantly higher mean ISS (22.6

± 14.1 vs. 13.5 ± 8.8; p = 0.001), lower RTS (6.6 ± 1.7 vs. 7.6 ± 0.9; p = 0.005) and TRISS scores (0.8681 ± 0.21 vs. 0.9713 ± 0.10; p = 0.01) and required more blood transfusion (43.8% vs. 25.7%; p = 0.03) than the normoglycemia group.

Table 1
Analysis of demographics, clinical presentation and outcome of trauma patients according to blood glucose level

	Overall (n = 250)	Normoglycemia n = 218 (87%)	Hyperglycemia* n = 32 (13%)	P-value
Age; years	35.1 ± 10.1	34.9 ± 10.1	36.7 ± 9.6	0.33
Males	245 (98.0%)	214 (98.2%)	31 (96.9%)	0.62
Body mass index	26.3 ± 11.1	25.8 ± 8.7	29.8 ± 20.9	0.29
Hs-TnT positive	49 (20.9%)	33 (16.2%)	16 (51.6%)	0.001
Fasting glucose after 24 h	7.25 (6.92–7.58)	6.9 (6.6–7.2)	9.2 (7.9–10.4)	0.001
Fasting glucose after 48 h	6.38 (6.13–6.63)	6.2 (5.9–6.4)	7.5 (6.4–8.6)	0.006
HbA1c %	5.61 (5.47–5.76)	5.4 (5.3–5.5)	6.9 (6.1–7.8)	0.003
Interleukin-6 (pg/ml)				
Baseline (on-admission)	137 (121–153)	122 (107–137)	240 (172–308)	0.001
Second day (after 24 h)	120 (101–138)	112 (93–131)	172 (109–236)	0.02
Third day (after 48 h)	108 (90–125)	94 (78–111)	193 (127–259)	0.008
Interleukin-18 (pg/ml)				
Baseline (on-admission)	305 (238–371)	299 (226–372)	369 (128–610)	0.11
Second day (after 24 h)	218 (199–236)	218 (197–238)	217 (186–248)	0.28
Third day (after 48 h)	215 (198–233)	211 (192–231)	242 (194–291)	0.05
Hs-C-reactive protein (ng/ml)				
Baseline (on-admission)	3.86 (3.45–4.26)	3.9 (3.4–4.3)	3.9 (2.7–5.1)	0.94
Second day (after 24 h)	9.50 (9.03–9.97)	9.4 (8.9–9.9)	10.1 (8.9–11.3)	0.46
Third day (after 48 h)	9.64 (9.14–10.13)	9.5 (9.0-10.1)	10.3 (9.0-11.5)	0.43

	Overall (n = 250)	Normoglycemia n = 218 (87%)	Hyperglycemia* n = 32 (13%)	P-value
Injury Severity score	14.7 ± 10.1	13.5 ± 8.8	22.6 ± 14.1	0.001
Revised Trauma score	7.45 ± 1.13	7.6 ± 0.9	6.6 ± 1.7	0.005
TRISS	0.9566 ± 0.1262	0.9713 ± 0.1011	0.8681 ± 0.2065	0.01
Hospital length of stay	8 (2-146)	8 (2–68)	12.5 (3-146)	0.001
ICU length of stay	4 (1–40)	4 (1–40)	6 (2–23)	0.04
Blood Transfusion	70 (28.0%)	56 (25.7%)	14 (43.8%)	0.03
Blood units transfused	2.5 (1–68)	2 (1–22)	6 (1–68)	0.03
Hospital complications	8 (3.2%)	6 (2.8%)	2 (6.3%)	0.29
Hospital mortality	12 (4.8%)	8 (3.7%)	4 (12.5%)	0.02
* random blood glucose ≥ 11.1 mmol/l at baseline, TRISS: trauma injury severity score				

The hyperglycemia group had prolonged ICU (p = 0.001) and hospital stay (p = 0.001). Patients with hyperglycemia had 3-times higher mortality than normoglycemia group (12.5% vs. 3.7%; p = 0.02).

Analysis of the 4 subgroups

The 4 trauma patients' groups were DH (n = 16), SIH (n = 16), diabetic normoglycemia (n = 11), and non-diabetic normoglycemia (n = 207) as shown in Table 2. Compared to the other 3 groups, patients with SIH were significantly younger (mean age 32 years), more obese, had severe injuries (mean ISS 24.5 ± 12.3); higher IL-6 levels at the 3 time points, prolonged hospital length of stay and higher mortality (p = 0.005). However, the 4 groups were comparable in terms of serum IL-18 and C-reactive protein levels at the different time points. Patients with diabetic hyperglycemia had higher hs-TnT and needed more units of blood transfusion. Higher shock index (> 0.8) was observed in both types of hyperglycemia compared to normoglycemic groups.

Table 2
comparative analysis of trauma patients based on the initial blood glucose and hemoglobin A1C

	NN (n = 207)	ND (n = 11)	SIH (n = 16)	DH (n = 16)	P
Age; years	34(33–36)	44(36–53)	32(28–36)	41(36–46)	0.001
Body mass index	26(24–27)	26(23–28)	34(19–50)	25(23–27)	0.030
Shock index	0.72(0.66–0.78)	0.71(0.55–0.87)	0.87(0.72–1.01)	0.88(0.69–1.07)	0.290
Injury Severity score	13(12–14)	19(10.5–28)	24.5(18–31)	21(12–29)	0.001
Revised Trauma score	8(7–8)	7(6–8)	6(5–7)	7(6–8)	0.001
GCS at ED	14(13–14)	12(9–15)	10(7–13)	12(9–14)	0.001
HbA1c %	5.3(5.2–5.4)	7.3(6.02–8.65)	5.2(4.95–5.37)	8.7(7.52–9.81)	0.001
Hs-TroponinT	17(9–26)	12(9–15)	49(15–81)	114(-56-285)	0.003
Interleukin-6 (pg/ml)					
on-admission	122(106–107)	130(55–204)	258(144–372)	222(135–308)	0.001
After 24 h	112(92–131)	123(51–195)	220(115–325)	125(49–201)	0.046
After 48 h	93(76–110)	113(20–207)	209(105–313)	176(83–269)	0.001
Interleukin-18(pg/ml)					
on-admission	301(229–373)	186(151–221)	200(153–246)	539(46-1031)	0.235
After 24 h	220(199–240)	233(151–315)	200(161–238)	235(184–287)	0.891
After 48 h	209(189–229)	244(150–338)	197(155–238)	288(200–376)	0.142
Hs-C-reactive protein (ng/ml)					
on-admission	3.9(3.4–4.3)	5.0(2.3–7.6)	4.3(2.1–6.5)	3.5(2.2–4.8)	0.642
After 24 h	9.6(9.1–10.1)	8.6(6.1–11.1)	10.6(9–12)	9.6(7.7–11.5)	0.601
After 48 h	9.6(9.0-10.1)	9(6–12)	10.9(9.3–12.4)	9.6(6.7-	0.576
TRISS	0.9733(0.96–0.99)	0.9359(0.85–1.01)	0.8207(0.67–0.97)	0.9092(0.82–0.99)	0.001

	NN (n = 207)	ND (n = 11)	SIH (n = 16)	DH (n = 16)	P
Blood Transfusion	26.1%	18.2%	56.3%	31.3%	0.062
Blood units transfused	3(3–4)	13(-101-127)	10(1–19)	18(-17-53)	0.002
Any surgical intervention	58%	45%	44%	44%	0.430
Hospital length of stay	12(10–14)	10(5–15)	26(7–44)	18(9–27)	0.003
ICU length of stay	6(4–7)	10(2–17)	10(6–14)	8(2–14)	0.106
Any hospital complications n = 8	2.9%	0%	6.3%	6.3%	0.709
Hospital mortality n = 12	2.9%	18.2%	18.8%	6.3%	0.005

NN:normoglycemia non-DM, ND:normoglycemia DM, SIH: stress induced hyperglycemia, DH: diabetic hyperglycemia, continuous variables are expressed as mean and 95% confidence intervals.

Figure 2 demonstrates the trend of inflammatory markers and blood glucose levels in trauma patients. The serum levels of IL-6, IL-18 and blood glucose increased after injury then showed a slowly decreasing trend, but did not reach baseline after 48 h.

Table 3 illustrates the bivariate correlation between blood glucose levels and other factors. Significant positive correlations were identified between initial blood glucose level and serum lactate ($r = 0.467$, $p = 0.001$), ISS ($r = 0.368$, $p = 0.001$), IL-6 ($r = 0.373$, $p = 0.001$) and hospital length of stay ($r = 0.304$, $p = 0.001$). Whereas, blood glucose levels showed significant negative correlations with base excess ($r=-0.417$, $p = 0.001$), GCS score ($r = -0.306$, $p = 0.001$), TRISS ($r = -0.310$, $p = 0.001$) and RTS ($r = -0.354$, $p = 0.001$). IL-6 correlated well with ISS ($r = 0.40$, $p = 0.001$).

Table 3
Bivariate correlation between blood glucose and other factors

Parameters	Pearson's correlation	P-value
Random glucose vs. WBC at ED	0.244	0.001
Random glucose vs. Lactate at ED	0.467	0.001
Random glucose vs. Base Excess at ED	-0.417	0.001
Random glucose vs. GCS at ED	-0.306	0.001
Random glucose vs. ISS	0.368	0.001
Random glucose vs. TRISS	-0.310	0.001
Random glucose vs. RTS	-0.354	0.001
Random glucose vs. Hospital LOS	0.304	0.001
Random glucose vs. Interleukin-6*	0.373	0.001
Random glucose vs. Interleukin-18*	0.108	0.09
Random glucose vs. Hs-CRP*	-0.059	0.35
*** baseline; RTS: revised trauma score; TRISS: trauma injury severity score; ISS: injury severity score; HsCRP: high sensitive C-reactive protein; ED: emergency department**		

Table 4 shows the laboratory parameters and outcomes based on ISS. Compared to mild and moderate injury, patients sustained severe injury (ISS $\geq$ 16) were more likely to have higher level of blood glucose, serum lactate, base excess and IL-6 ($p = 0.001$ for all). However, the mean serum levels of IL-18 and hs-CRP, at three time points, did not significantly differ among the ISS groups.

Table 4
Presentation of inflammatory markers and glucose level based on injury severity score (ISS)

Parameters	Mild (ISS ≤ 8) n = 53	Moderate (ISS 9–15) n = 112	Severe (ISS ≥ 16) n = 84	P value
Blood glucose level				
Random (on admission)	7.21 ± 1.66	8.05 ± 2.69	9.59 ± 3.45	0.001
Fasting (after 24 h)	6.65 ± 1.41	6.99 ± 1.75	7.85 ± 3.05	0.004
Fasting (after 48 h)	6.11 ± 1.30	6.36 ± 1.46	6.49 ± 2.17	0.48
HbA1c %	5.35 ± 0.55	5.61 ± 1.14	5.76 ± 1.44	0.14
Serum lactate				
Baseline (on-admission)	2.71 ± 1.34	2.71 ± 1.11	3.29 ± 1.77	0.01
Second day (after 24 h)	1.82 ± 0.95	1.64 ± 0.85	2.18 ± 1.86	0.02
Third day (after 48 h)	1.22 ± 0.72	1.25 ± 0.52	1.48 ± 1.45	0.24
Base Excess				
Baseline (on-admission)	-2.01 ± 3.06	-1.85 ± 2.45	-4.67 ± 4.19	0.001
Second day (after 24 h)	-0.75 ± 2.00	-0.72 ± 2.46	-3.03 ± 3.84	0.001
Third day (after 48 h)	1.40 ± 2.34	1.01 ± 2.53	-1.79 ± 4.50	0.001
Interleukin-6				
Baseline (on-admission)	61.4 (5.8-510.3)	75.9 (4.8-595.9)	146.6 (4.02–627.1)	0.001
Second day (after 24 h)	47.6 (3.1-374.1)	48.6 (6.7-722.7)	85.6 (5.3-1109.3)	0.001
Third day (after 48 h)	37.3 (2.4-547.9)	48.6 (1.9–550.0)	74.5 (3.2–550.0)	0.04
Interleukin-18				
Baseline (on-admission)	191.6 (51.9-1214.3)	186.8 (32.4-3890.9)	197.5 (45.0-5000.0)	0.94
Second day (after 24 h)	184.9 (50.6-1328.9)	183.5 (41.3-739.9)	211.1 (47.1-737.4)	0.20
Third day (after 48 h)	170.3 (30.3-785.6)	178.5 (1.04–947.9)	197.7 (55.0-705.1)	0.07

Parameters	Mild (ISS ≤ 8) n = 53	Moderate (ISS 9–15) n = 112	Severe (ISS ≥ 16) n = 84	P value
hs-CRP				
Baseline (on-admission)	3.05 (0.06–13.1)	3.09 (0.18–13.5)	3.35 (0.03–12.8)	0.55
Second day (after 24 h)	10.8 (0.8–14.9)	10.8 (0.007–14.9)	10.6 (0.09–13.9)	0.22
Third day (after 48 h)	10.9 (0.02–15.5)	10.9 (0.004–14.3)	10.7 (0.2–14.9)	0.56
All-complications	1 (1.9%)	0 (0.0%)	7 (8.3%)	0.004
Hospital LOS	6.0 (2–62)	6.5 (2–68)	11.5 (2-146)	0.001
In-hospital mortality	0 (0.0%)	0 (0.0%)	12 (14.3%)	0.001

Logistic regression analysis showed that on- admission blood glucose had age-sex-GCS adjusted odd ratio 1.20 (95% CI 1.06–1.33, p = 0.003) for severe injury and 1.08 (95% CI 0.91–1.23, p = 0.35) for hospital mortality.

Discussion

This is a prospective study to identify the patterns and effect of initial hyperglycemia and inflammatory biomarkers in trauma patients. Up to our knowledge, the constellation of on-admission random blood glucose, proinflammatory cytokines and injury severity among trauma patients is understudied. There are several key findings of this study. Almost 13% of trauma patients had on- admission hyperglycemia; half of them had SIH. Hyperglycemic patients showed higher association with elevated IL-6, IL-18 and hs-CRP compared to the normoglycemic patients. Also, patients with hyperglycemia were more likely to have severe injuries, prolonged hospitalization and higher mortality than normoglycemic patients. Moreover, IL-6 level was greater in SIH (non-diabetic) compared to DH group. Logistic regression analysis showed that adjusted on-admission blood glucose was predictor for injury severity and not for hospital mortality.

Initial readings of IL-6 correlated significantly with the ISS. The blood glucose levels showed significant correlation with serum IL-6, serum lactate, ISS, and length of hospitalization. Also, we found an association between hyperglycemia and hs-TnT. Prior works revealed a significant association between the severity of trauma and positivity of hs-TnT as a reflection of traumatic stress [21, 22]. Also, trauma patients with hyperglycemia presented with a higher shock index (> 0.8) which indicates worse presentation and outcome [23, 24].

The current study demonstrated that patients with SIH had a 3-fold higher rate of mortality as compared to those with DH. These findings are in accordance with earlier studies which showed significantly greater

risk of mortality in patients with SIH as opposed to those who had DH [11, 15, 17, 25].

A recent study on thoracoabdominal injury patients demonstrated a higher rate of mortality in nondiabetic patients with on- admission hyperglycemia as compared to those with initial normoglycemia [26]. Furthermore, a prospective observational study of traumatic brain injury (TBI) reported a marked hyperglycemia in patients with severe TBI which independently predicted the poor short-term neurological outcome [27].

Prior studies showed a relationship between serum cortisol, catecholamine levels and severity of injury. Patients with severe injuries were more likely to develop SIH [5, 28–30]. Consistent with these observations, hyperglycemia patients in our cohort had a higher injury severity as compared to normoglycemic patients.

In our study, the overall complications were higher in both types of hyperglycemia compared to normoglycemia groups, but the difference did not reach statistical significance. A prior study reported that initial hyperglycemia in trauma patients correlated with serum lactate and ISS and was associated with higher mortality; however, the rate of infection was not significantly higher [31].

In our patients, the increase in hs-CRP was detected after 24 h of trauma and reached its peak value at 48 h. Giannoudis et al., [32] reported that serum CRP levels were within the normal range on the initial presentation which then gradually increased and reached the peak value on the third day post-trauma. The authors also found an association between ISS and IL-6 levels but such association was not observed with CRP. Consistent with our study, earlier studies reported a significant correlation between higher ISS and IL-6 level on the initial presentation [33–35]. We also observed a higher level of Il-18 in DH in comparison to the other groups including SIH (but statistically non-significant); a finding that needs further explanation [36]. Our study performed serial measurements of blood glucose and cytokines to understand the complex relationship between hyperglycemia and inflammatory response in trauma. These findings indicated that immunoneuroendocrine alterations might be involved in the pathophysiology of trauma patients [16].

Limitations

The first limitation is that patients with DH may have also some degree of stress response which was underestimated. Second, we could not measure the levels of stress response hormones or catecholamines. Third, selection bias cannot be ignored along the study period. In the emergency department, we were using sliding scale insulin for patients with hyperglycemia; however, we did not measure the effect of exogenous insulin on the cytokine's levels. Apart from the significant difference in age, we could not explain the mortality rate in the normoglycemic diabetic group which was relatively similar to that of the SIH. Finally, the HbA1c level might not be accurate in patients necessitate early blood transfusion; as transfusion may alter the HbA1c reading [37–38].

In **conclusion**, patients with on-admission hyperglycemia have more severe injury and worse hospital outcome compared to normoglycemia patients. The initial blood glucose correlates with serum IL-6 which indicates a potential role of the systemic inflammatory response in the disease pathogenesis among severely injured patients. On-admission glucose level could be a useful marker of injury severity, triage and risk assessment in trauma patients. These observations warrant further evaluation in larger multicenter studies.

List Of Abbreviations

ISS: injury severity score

hs-CRP: high sensitive reactive protein

IL: interleukin

HbA1c: glycosylated hemoglobin

SIH: stress induced hyperglycemia

Declarations

Ethics approval and consent to participate: The Institutional Review Board (IRB# 14471/14) of Hamad Medical Corporation has approved this study. This study is registered at the ClinicalTrials.gov (Identifier: NCT02999386).

Consent to publish not applicable.

Availability of data and material: all data were shown in the study analysis and tables. Further data need approval from the Qatar national trauma registry and medical research center (contact: mrcinfo@hamad.qa).

Competing interests: none

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Author contribution: all authors have contributed substantially in the study design, data collection, data interpretation, writing draft, reviewing and approval of the manuscript.

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Figures

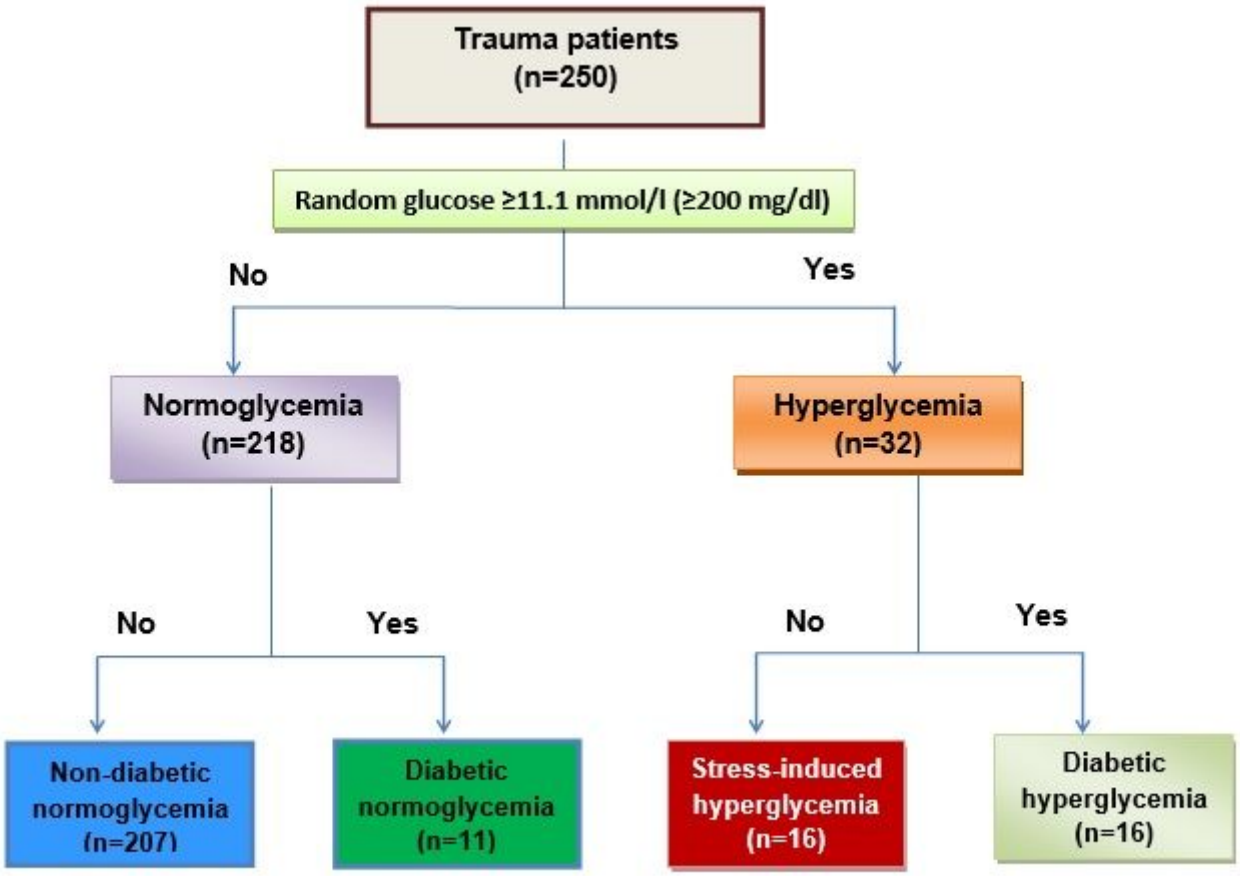

Figure 1

Study design

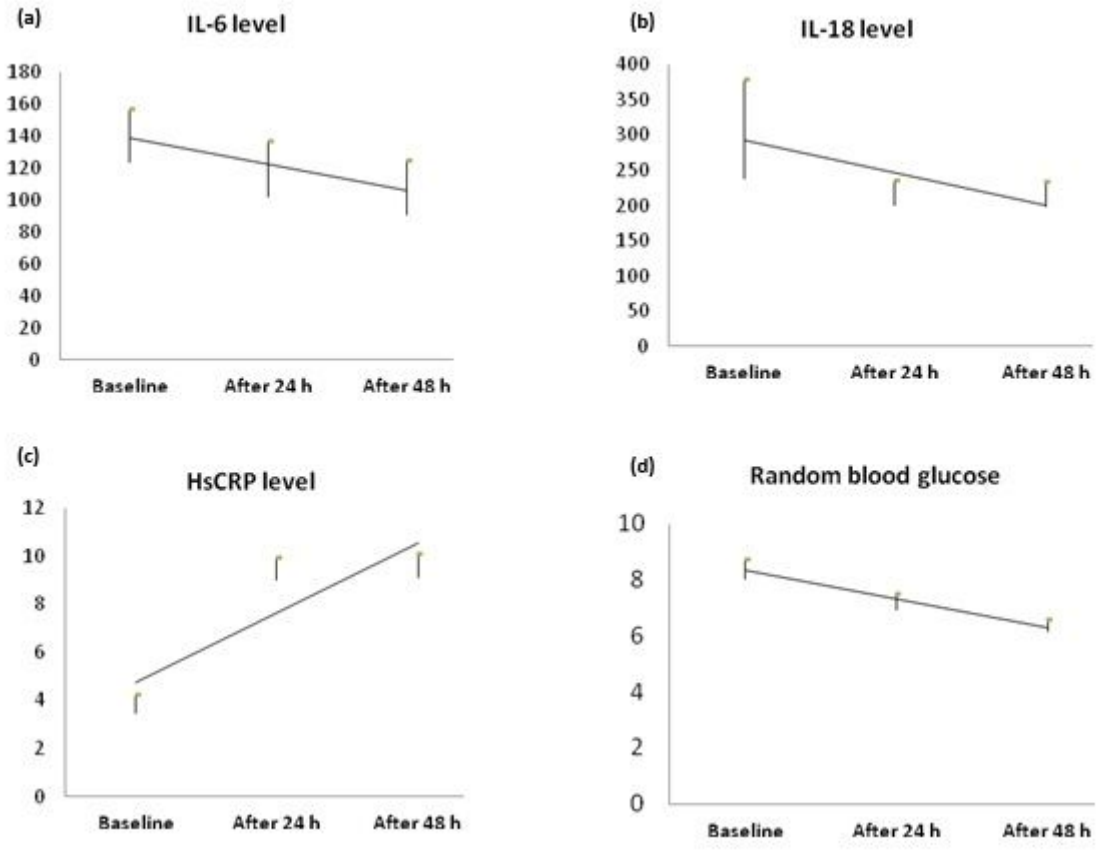

Figure 2

Trend of inflammatory markers and blood glucose levels in the overall trauma patients (a) IL-6; (b) IL-18 (c) HsCRP (d) random blood glucose