

ADMISSION HYPERGLYCEMIA IN CRITICALLY ILL PATIENTS WITH SEPSIS; HIGH IL6 AND ITS RELATION WITH OUTCOME

By

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ABSTRACT

Background: Hyperglycemia has long been recognized as a common occurrence in critically ill patient, even without history of diabetes mellitus (D.M). Although there are few studies investigating the prevalence of stress hyperglycemia, one study reported that 38% of patients admitted to general hospitals had hyperglycemia episodes, 16% of which had no previous history of D.M.

Objective: To investigate the role of high IL6 in patients with sepsis admitted to medical I.C.U with acute hyperglycemia and its relation to 30 days outcome.

Patients and Methods: This study was conducted on 100 adult septic patients who were admitted to medical I.C.U at Al-Hussein University Hospital, the study was carried in the period between January 2018 and June 2019. 80 patients with evidence of hyperglycemia and 20 patients with euglycemic state.

Results: non-significant difference was found according to mean values of Na⁺, K⁺, creat, TLC, HB%, PLT, ALT, AST. On the other hand, the hyperglycemic group showed a significant increase regarding mean value of HbA1c compared to control group. The comparative study between the 2 groups revealed a significant increase of mean value of CRP in the hyperglycemic group compared to the control group. As regards the vital signs, the hyperglycemic group showed a significant increase in mean values of systolic blood pressure, diastolic blood pressure, MAP & HR compared to the control group. While there was no significant difference between the 2 groups regarding temperature and RR. This study showed statistically significant decrease in mean values of GCS in hyperglycemic group compared to control group, while APACHE II and qSOFA showed a significant increase in hyperglycemic group compared to control group. The mean values of ABG parameters revealed no statistically significant difference between the 2 groups. On the other hand, mean values of RBS and IL6 showed a statistically significant increase in hyperglycemic group compared to control group. The comparative study between the 2 groups showed a significant increase in mean values of hyperglycemic group compared to control group according to duration of ICU stay (days), Insulin therapy, AKI and Outcome and non-significant difference according to ILD, CLD, CKD, stroke, pneumonia, IHD, COPD & HF.

Conclusion: Stress hyperglycemia with high IL6 is strongly associated with adverse outcomes in patients with sepsis who were admitted to the medical ICU. Sepsis patients with hyperglycemia showed increased incidence of mortality and AKI.

Key words: Hyperglycemia, sepsis, ICU, IL6.

INTRODUCTION

Hyperglycemia has long been recognized as a common occurrence in critically ill patient, even without history

of diabetes mellitus (D.M). Although there are few studies investigating the prevalence of stress hyperglycemia, one study reported that 38% of patients

admitted to general hospitals had hyperglycemia episodes, 16% of which had no previous history of D.M (*Fayed et al., 2015*).

Stress hyperglycemia is usually defined as newly detected hyperglycemia > 200 mg/dl which resolve after resolution of acute illness. Two diagnostic categories of stress hyperglycemia have been reported: Hospital related hyperglycemia according to (ADA) consensus definition F.B.S ≥ 126 mg/dl or R.B.S > 200 mg/dl without evidence of previous D.M. Pre-existing D.M with deterioration of pre-illness glycemic control (*Pakhetra et al., 2016*).

Stress hyperglycemia is thought to be the body's adaptive response to stress on injury. However, recently it has been found that hyperglycemia in critically ill patients can pose a greater risk of mortality and morbidity. Furthermore, the evidence suggests that insulin therapy to control stress hyperglycemia can reduce mortality and improve overall patient outcome (*Robba and Bilotta, 2016*).

Hospital related hyperglycemia results from activation of insulin counter regulatory hormones caused by stress. Glycemic control is further impaired by administration of drugs which increase insulin resistance such as catecholamines and steroids.

Severe hyperglycemia is a catabolic state associated with adverse electrolytes and volume shifts. Mechanisms include high tissue and circulatory concentrations of inflammatory cytokines and reduction of glucose uptake capacity in peripheral tissues (*Pakhetra et al., 2016*).

There is increased hepatic glucose production, depressed glycogenesis and glucose intolerance. Increased production of counter regulatory hormones lead to increased insulin resistance, thereby decreasing insulin action (*Nakamura et al., 2012*).

TNF and IL6 have been shown to have a role in insulin resistance most likely via the modification of signaling properties of insulin receptor substrates.

Insulin resistance ultimately promote a catabolic state leads to lipotoxins which further aggravate the inflammatory state especially in critical ill patients (*Dellinger et al., 2013*).

The present work aimed to investigate the role of insulin resistance in patients with sepsis admitted to medical I.C.U with acute hyperglycemia and its relation to 30 days outcome.

PATIENTS AND METHODS

This study was a prospective study, which was conducted on 100 adult sepsis patients who were admitted to medical I.C.U at Al-Hussein University Hospital, the study was carried in the period between January 2018 till June 2019. 80 patients with evidence of hyperglycemia and 20 patients with euglycemic state. The study included patients ≥ 18 and < 65 years old; where patients receiving steroid therapy or/and already started steroid on admission.

At enrollment, patients were subjected to the following: history taking and clinical examination, laboratory work-up, blood sugar level, C-peptide, IL6, Hb A1c, serum CRP, CBC, ABG, kidney function tests and liver function tests.

The diagnosis of sepsis depended on the definition of a college of chest physician/ society of critical care medicine consensus conference (*Chakraborty et al., 2020*) by an identifiable site of infection and evidence of systemic inflammatory response.

Admission hyperglycemia was defined as the first measurement of glucose within a time window of 4 hours before and up to 4 hours after admission. Blood glucose was categorized as: Euglycemia (70-140 mg/dl), mild hyperglycemia (141-199 mg/dl) and severe hyperglycemia ≥ 200 mg/dl (*Pakhetra et al., 2016*).

Assessment of sepsis was done according to:

APACHE II score: (*Park et al., 2010*).

qSOFA score: (*Raith et al., 2017*).

IL6: Enzyme immunoassay for the quantitative determination of circulating

IL6 concentrations in human serum (*RIEDEL et al., 2005*).

Statistical analysis:

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean \pm standard deviation (SD). Qualitative data were expressed as frequency and percentage. Independent-samples t-test of significance was used when comparing between two means mann whitney U test. Chi-square (x²) test of significance was used in order to compare proportions between qualitative parameters. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant when : P-value ≤ 0.05 .

RESULTS

This prospective study enrolled 100 adult sepsis patients who were admitted to medical I.C.U. They were divided into control group of 20 cases with euglycemic state, and study group of 80 cases with hyperglycemic state. Statistically

significant difference was found between groups according to demographic data and ABG, but showed statistically significant increase in mean of hyperglycemia group compared to control group according to CRP (**Table 1**).

Table (1): Comparison between control group and hyperglycemic group according to demographic data, CRP and ABG

Demographic data \ Groups	Control Group (n=20)	Hyperglycemic Group (n=80)	p-value
Age (years)#			
Mean±SD	54.45±9.93	53.33±8.61	0.615
Range	33-64	23-65	
Sex†			
Female	11 (55.0%)	32 (40.0%)	0.226
Male	9 (45.0%)	48 (60.0%)	
C-reactive protein‡			
Median (IQR)	170 (65)	150 (90)	0.037
Range	45-309	6-395	
Arterial blood gases			
PaO₂ (mmhg)‡			
Median (IQR)	63 (15)	65 (19)	0.651
Range	43-90	16-99	
PH#			
Mean±SD	7.37±0.10	7.28±0.18	0.034
Range	7.14-7.47	6.8-7.69	
Paco₂ (mmhg)‡			
Median (IQR)	37 (11)	38 (22)	0.929
Range	16-55	12-188	
HCO₃ (meq/L)‡			
Median (IQR)	23 (8)	21 (7)	0.245
Range	14.9-40	4.3-36	

Using: #Independent Sample t-test; †Chi-square test; ‡Mann-Whitney test

A statistically significant increase was found in mean of hyperglycemic group

compared to control group according to HbA1c (**Table 2**).

Table (2): Comparison between control group and hyperglycemic group according to lab. Chemistry

Lab chemistry	Groups	Control Group (n=20)	Hyperglycemic Group (n=80)	p-value
Na⁺ (meq/L)#				
Mean±SD		137.45±9.81	138.21±5.87	0.66
Range		128-172	128-150	
K⁺ (meq/L)#				
Mean±SD		3.94±0.55	4.20±1.36	0.407
Range		3.1-5.2	2.7-9.9	
Creatinine (mg/100m)‡				
Median (IQR)		3 (2)	3 (3)	0.671
Range		0.6-6.9	0.5-13	
Total leukocytic count (TLC) (cmm3)#				
Mean±SD		17.36±3.79	17.12±4.96	0.841
Range		13.3-28	12-34.5	
Hb A_{1c}‡				
Median (IQR)		5 (1.5)	7 (2)	0.002
Range		3.9-6.3	2.4-10.5	
HB%‡				
Median (IQR)		10 (4)	10 (3)	0.823
Range		2.2-15	3.7-17	
Platelets (cmm3) ‡				
Median (IQR)		225 (111)	224 (110)	0.853
Range		85-490	70-435	
Alanine transaminase (ALT) (U/L)‡				
Median (IQR)		77 (80)	62 (101)	0.594
Range		10-319	10-450	
Aspartate transaminase (AST) (U/L)‡				
Median (IQR)		90 (140)	81 (115)	0.417
Range		16-452	10-466	

Using: #Independent Sample t-test; ‡Mann-Whitney test

A statistically significant decrease was found in mean of hyperglycemic group compared to control group according to GCS, while APACHE II and qSOFA

showed a statistically significant increase in hyperglycemic group compared to control group (**Table 3**).

Table (3): Comparison between control group and hyperglycemic group according to scoring system

Scoring system \ Groups	Control Group (n=20)	Hyperglycemic Group (n=80)	p-value
Glasgow Coma Score (GCS) #			
Mean±SD	12.25±0.97	9.85±1.63	<.0001
Range	11-14	5-12	
APACHE II#			
Mean±SD	15.75±2.63	22.85±4.31	<.0001
Range	12-21	10-37	
qSOFA#			
Mean±SD	1.75±0.72	2.75±0.44	<.0001
Range	1-3	2-3	

Using: #Independent Sample t-test

There was a statistically significant increase in mean of hyperglycemic group compared to control group according to RBS and serum level of IL6 (**Table 4**).

Table (4): Comparison between control group and hyperglycemic group according to RBS and IR

Variables \ Groups	Control Group (n=20)	Hyperglycemic Group (n=80)	p-value
Random blood sugar (RBS) (g/dL) ‡			
Median (IQR)	106 (16)	410 (115)	<0.001
Range	76-136	180-605	
Serum level of (IL6) ‡			
Median (IQR)	0.06 (0.45)	1.3 (1.5)	<0.001
Range	0.0099-0.1	0.04-4.6	

Using: #Independent Sample t-test; ‡Mann-Whitney test

A statistically significant increase was found in mean of hyperglycemic group compared to control group according to duration of ICU stay (days), Insulin therapy, AKI and hypoglycemia and outcome (**Table 5**).

Table (5): Comparison between control group and hyperglycemic group according to outcome

Outcome†	Groups	Control Group (n=20)	Hyperglycemic Group (n=80)	p-value
Duration of ICU stay (days)#				
Mean±SD		9.80±4.24	14.74±6.90	0.003
Range		1-21	6-67	
Insulin therapy		2 (10.0%)	32 (40.0%)	0.023
Acute kidney injury (AKI)		0 (0%)	14 (17.5%)	0.039
Interstitial lung disease (ILD)		1 (5.0%)	15 (18.8%)	0.134
Chronic lung disease (CLD)		2 (10.0%)	19 (23.8%)	0.177
Chronic kidney disease (CKD)		4 (20.0%)	6 (7.5%)	0.096
Stroke		1 (5.0%)	5 (6.3%)	0.833
Pneumonia		2 (10.0%)	1 (1.3%)	0.04
Ischemic heart disease (IHD)		1 (5.0%)	9 (11.3%)	0.405
Chronic obstructive pulmonary disease (COPD)		1 (5.0%)	9 (11.3%)	0.405
Heart failure (HF)		1 (5.0%)	0 (0.0%)	0.144
Outcome				
Alive		19 (95.0%)	56 (70.0%)	0.021
Died		1 (5.0%)	24 (30.0%)	
Normal		9 (45.0%)	2 (2.5%)	<0.001

Using: #Independent Sample t-test; †Chi-square test

DISCUSSION

Hyperglycemia has long been recognized as a common occurrence in critically ill patient, even without history of D.M. Stress hyperglycemia is usually defined as nearly detected hyperglycemia > 200 mg/dl which resolve after resolution of acute illness (Fayed *et al.*, 2015).

This study demonstrated that there was no statistically significant difference between groups according to age and sex. On the other hand, the study group showed a significant increase regarding CRP compared to the control group. Dellinger *et al.* (2013) showed that inflammatory markers such as CRP have been related to the development of insulin resistance and type 2 diabetes (Sourris *et al.*, 2012). Ford E. had also established

that CRP levels are higher in people with diabetes and associated with increased HbA1c in people without diabetes.

Dellinger *et al.* (2013) go a step further with the finding that among people with established diabetes, at successively higher levels of HbA1c the percent of people with CRP > 0.30 mg/dl is significantly higher. The mean implications of these findings are that inflammation may not only be implicated in the development of diabetes, but also in ongoing levels of hyperglycemia once diabetes is established.

Jozwiak *et al.* (2011) found links between CRP and insulin resistance, other study has related hyperglycemia to inflammation by demonstrating simultaneous inflammation, endothelial

dysfunction and insulin resistance at the physiologic level.

In the current study, hemodynamic parameters, presence of risk factors and comorbid diseases, revealed those patients with hyperglycemia had lower SBP and DBP. These results were in agreement with *Schmitz et al. (2012)* who found that when the severity of disease increases in sepsis, the variability in the values of both SBP and DBP are increased. Also he found that APACHE II score was positively correlated with variability in the values of both SBP and DBP. This indicated that when APACHE II increased, blood pressure varied too.

Also, the comparison between the two groups revealed that HR was higher in patients of the hyperglycemic group. These results agreed with *Knaus et al. (2010)* who concluded that, variability in HR was correlated with increased illness severity as calculated using APACHE II score.

In agreement with *Shigeki et al. (2013)*, our results illustrated that elevated temperature was not associated with an increase in disease severity or risk of mortality.

According to RR and ABG, this study showed no significant difference between the two groups. These results were explained by *Ganesh et al. (2016)* who mentioned that in patients with sepsis and septic shock, high anion gap metabolic acidosis is the dominant blood gas anomaly in addition to lactate.

This study also showed that patients with hyperglycemia had a significant lower GCS which may be explained by severity of sepsis in those patients. This

was in agreeing with *John and Bryan (2011)* who proved that advanced sepsis can cause brain damage. Milder cases may recover without neurological problem; these cases may be related to the reversible mechanisms of what is called sepsis-associated encephalopathy (SAE), however more advanced cases of sepsis may have neuron-killing complications.

In this study, data of disease severity which is represented by hemodynamic parameters, need of mechanical ventilation and vasoactive support were significantly worse in hyperglycemic group which was reflected also in worse APACHE II score. This was in agree with *James (2010)* who proved that sepsis ultimately leads to tissue injury and multi-organ dysfunction for example, circulatory shock and acute lung injury.

The present study showed a significant increase in the level of plasma IL6 in the hyperglycemic patients compared to the control group this also what was proved by *Nakamura et al. (2012)* who made a study on 40 patients with sepsis admitted to ICU. In this study he noticed elevation in serum IL-6 level in SIRS/ sepsis patients and the levels were extremely high in patients with severe hyperglycaemia and severe septic shock *Nakamura et al. (2012)* concluded that measurement of serum IL-6 level is useful in evaluating the severity and in predicting the outcome of patients with sepsis *Jozwiak et al. (2011)*.

Our study showed statistically significant increase mean of hyperglycemia group compared to control group according duration of ICU stay. In support, *Marik and Bellomo (2013)* mentioned that the median duration of

ICU and hospital length of stay was longer in patients with stress hyperglycemia. They added that severe stress hyperglycemia may be harmful due to its effects on serum osmolarity. In addition, severe hyperglycemia exceeds the renal threshold, resulting in an osmotic diuresis and volume depletion.

In terms of AKI, this study reported a higher incidence in hyperglycemic patients. This was in agree with *Wang et al. (2017)* who explained that stress hyperglycemia can impair renal function by increased activation of NF-kappa B and oxidant levels with the stages of sepsis, which leads to a much higher incidence of AKI.

Our study clarified that septic patients with hyperglycemia had a significant higher mortality rate. Several studies have demonstrated that sepsis is associated with the activation of inflammation and coagulation, and the activation of coagulation accounts for a large proportion of deaths. In addition, stress hyperglycemia is associated with abnormal coagulation and fibrinolysis to a certain extent *Wang et al. (2017)*.

Venot et al. (2015) showed higher mortality in hyperglycemic patients. The functions of leucocytes, especially polymorphonuclear leukocytes (PMN), are impaired by hyperglycemia. It was reported by several studies that membrane fluidity of PMN were significantly lower in hyperglycemic patients, resulting in the decrease of multiple functions, such as impaired migration, reduced phagocytosis, and intracellular killing capacity, as well as altered chemotaxis.

CONCLUSION

The results of our study suggested that stress hyperglycemia with high IL6 is strongly associated with adverse outcomes in patients with sepsis who were admitted to the medical ICU. Septic patients with hyperglycemia showed increased incidence of mortality and AKI.

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إرتفاع سكر الدم الحاد ومستوي الانترلوكين السادس في الحالات الحرجة لمرضى التسمم الدموى وعلاقته بالنتائج

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خلفية البحث: فرط سكر الدم لفترة طويلة حدث شائع في المرضى المصابين بأمراض حرجة، حتى بدون تاريخ مرضى للإصابة بمرض السكر.

الهدف من البحث: التحقيق في دور الانترلوكين السادس في المرضى الذين يعانون من تسمم الدم المعترف بهم في وحدة العناية المركزة الطيبة مع ارتفاع السكر في الدم الحاد وعلاقته بنتيجة 30 يوماً.

المرضى وطرق البحث: أجريت هذه الدراسة على 100 مريض بالغ مصاب بتسمم الدم تم إدخالهم إلى وحدة العناية المركزة الطيبة، و80 مريضاً لديهم دليل على ارتفاع السكر في الدم و20 مريضاً يعانون من حالة سكر الدم.

نتائج البحث: هناك اختلاف غير ذي دلالة وفقاً لمتوسط القيم للصدوديوم والبوتاسيوم والكرياتينين وعدد كرات الدم البيضاء والنسبة المئوية للهيموجلوبين وعدد الصفائح الدموية وإنزيمات الكبد. من ناحية أخرى، أظهرت مجموعة ارتفاع السكر في الدم زيادة كبيرة فيما يتعلق بالقيمة المتوسطة للهيموجلوبين السكري مقارنة بالمجموعة الضابطة. كشفت الدراسة المقارنة بين المجموعتين زيادة كبيرة في متوسط القيمة للبروتين التفاعلي سى في مجموعة ارتفاع السكر في الدم مقارنة بالمجموعة الضابطة. فيما يتعلق بالعلامات الحيوية، أظهرت مجموعة فرط سكر الدم زيادة كبيرة في متوسط القيم لضغط الدم الانقباضي وضغط الدم الانبساطي ومتوسط الضغط الشرياني ومعدل نبض القلب مقارنة بالمجموعة الضابطة. بينما لم يكن هناك فرق كبير بين المجموعتين فيما يتعلق بدرجة الحرارة ومقاومة الإنسولين.

وقد أظهرت هذه الدراسة انخفاضاً مهماً إحصائياً في متوسط القيم على مقياس جلاسكو للغيوبية في مجموعة ارتفاع السكر في الدم مقارنة بالمجموعة

الضابطة، في حين أظهرت الدرجات على مقياس وظائف الأعضاء الحادة و الصحة المزمنة ومقياس سريع لتقييم فشل الأعضاء المرتبط بتسمم الدم زيادة كبيرة في مجموعة ارتفاع السكر في الدم مقارنة بالمجموعة الضابطة. لم تكشف القيم المتوسطة لغازات الدم الشرياني عن فرق ذي دلالة إحصائية بين المجموعتين. من ناحية أخرى، أظهرت قيم متوسط مستوى السكر العشوائي بالدم ومستوي الانترلوكين السادس بالدم زيادة ذات دلالة إحصائية في مجموعة ارتفاع السكر في الدم مقارنة بالمجموعة الضابطة. أظهرت الدراسة المقارنة بين المجموعتين زيادة كبيرة في متوسط القيم لمجموعة ارتفاع السكر في الدم مقارنة بالمجموعة الضابطة وفضلاً لمدة بقاء وحدة العناية المركزة (أيام) والعلاج بالإنسولين والفشل الكلوي الحاد والنتائج وفرق غير مهم وفضلاً لالتهاب رئوي خلوي مزمن والأمراض الرئوية المزمنة وأمراض الكلى المزمنة والسكتة الدماغية والالتهاب الرئوي ومرض القلب الإقفاري وفشل عضلة القلب المزمن والانسداد الرئوي المزمن.

الاستنتاج: فرط سكر الدم مع ارتفاع مستوي الانترلوكين السادس بالدم يرتبطان بقوة بالنتائج السلبية في المرضى الذين يعانون من تسمم الدم الذين تم إدخالهم إلى وحدة العناية المركزة الطبية. وأظهر مرضى تسمم الدم الذين يعانون من ارتفاع السكر في الدم زيادة في حدوث الوفيات وفشل كلوي حاد.

الكلمات الدالة: ارتفاع سكر الدم – التسمم الدموي – إنترليوكين 6- العناية المركزة .