PLASMA INTERLEUKIN-6 LEVELS MAY BE ASSOCIATED WITH THE LENGTH OF STAY TIME OF ADULT HYPERGLYCEMIC PATIENTS IN AN INTENSIVE CARE UNIT

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Abstract

Context. Estimation of intensive care unit (ICU) length of stay time (LOS) may be challenging, and pro-inflammatory cytokines can be used as a marker for this purpose.

Objective. The current study aimed to investigate the association between pro-inflammatory cytokine levels and LOS in hyperglycemic patients admitted to adult ICU.

Design. This is a prospective observational study.

Subjects and Methods. All adult ICU patients with a blood glucose level higher than 250 mg/dL, during the study period were included. Hospitalization day demographics were recorded, and plasma IL-6, IL-1 β , and TNF- α concentrations were measured.

Results. A total of 74 patients were enrolled in the study. Diabetic ketoacidosis (DKA) was positive in 31 patients, and the remaining 43 were in the non-DKA (NDKA) group. There was no difference between the two groups in terms of age, gender, LOS, hemoglobin, hematocrit, lactate levels, and platelets count. IL-6, IL-1 β , and TNF- α levels did not show any difference between DKA and NDKA groups ($p=0.784$, 0.413 , and 0.288 , respectively). There was a positive correlation between IL-6 levels and LOS ($n=74$, Pearson correlation= 0.330 ; $p=0.004$).

Conclusions. Among pro-inflammatory cytokines, IL-6 showed a better performance for the prediction of LOS than IL-1 β , TNF- α , and CRP.

Keywords: Cytokine, Interleukin-6, Intensive care unit, Length of stay time, Hyperglycemia.

INTRODUCTION

It has been shown that cytokines are responsible for the cellular and humoral immune system as well as physiologic responses that can be summarized as hematopoiesis, regulation of inflammation, and cellular proliferation and differentiation. Interleukins (ILs) are a subgroup of the cytokine family and play an important

role in the regulation of these complex mechanisms (1). IL-6 is a cytokine that acts through gp130-containing receptors, and it plays the most important role in the acute phase response to infection and injury (1-3). Globally, gp130-STAT3-dependent action triggers the adaptive immune response, but its local effect is tissue remodeling and cell infiltration (4). Additionally, in the acute phase response, IL-6 primarily activates the lymphocytes and regulates Th17 immune deviation (1).

However, the mechanism through which IL-6 causes these effects is not clearly defined. Leukocytosis in the acute hyperglycemic state can occur without concomitant infections or febrile conditions, which may be associated with the increased sympathetic activity that results in elevated serum IL-6 levels (5, 6). It has been shown that blood levels of IL-6 have a correlation with insulin resistance, and a significant increase of IL-6 levels has been observed in both type 1 and type 2 diabetes mellitus (DM) patients (7-10). Elevated serum IL-6 levels have been shown to be associated with DKA, acute hyperinsulinemia, lipid peroxidation, and platelet activation (11-13). Diabetic ketoacidosis (DKA) may trigger an immunologic response and mediate IL-1 β , TNF- α , and IL-6 release from monocytes (14-16). Elevated IL-1 β , TNF- α , and IL-6 levels have been shown to return to normal levels after the treatment of the hyperglycemic crisis, which was attributed to the anti-inflammatory effect of insulin (5, 14). Cytokine regulation in patients with DM is very important because DKA risk is increased in the loss of cytokine regulation, and the treatment mediates the immune response (15, 17). Besides the acute phase, IL-6 signalling is thought to be associated with chronic complications of uncontrolled DM such as diabetic nephropathy and sepsis (4, 18, 19).

Excessive inflammatory response in intensive

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care unit (ICU) patients may be associated with prolonged length of stay (LOS) and expansion of costs, mortality, and morbidity, and the prediction of LOS can be challenging (20). As with other ICU patients, hospitalization of DKA patients in the ICU may increase the cost of care, and several studies predict mortality and LOS before admission (21-23). Proper treatment of hyperglycemia with insulin and amendment of hyperglycemia is expected to improve outcomes in ICU patients primarily through the salubrious effect of insulin (24). IL-6 has been shown to be associated with LOS in trauma patients (25). Recently, higher pre-admission IL-6 levels were found to be associated with higher severity scores and worsened short-term outcomes in community-acquired pneumonia (CAP) patients (26).

To the best of our knowledge, the relationship between the LOS of hyperglycemic ICU patients and pre-admission levels of pro-inflammatory cytokines has not been reported before. In this study, we aimed to investigate the association between pro-inflammatory cytokine levels and ICU LOS time in hyperglycemic patients.

MATERIALS AND METHODS

This is a prospective observational study. The local ethical committee of the Bagcilar Training and Research Hospital approved the study prior to data collection (approval number was 2014/182). Informed consent was obtained prior to the study, and demographics were recorded from patient charts.

Diagnosis of DKA was mainly based on laboratory findings. We included all the patients ≥ 18 years old and admitted to the ICU from the emergency department with a blood glucose level higher than 250 mg/dL (13.9 mmol/L) during the study period. Patients with acidosis ($\text{pH} < 7.3$) and low bicarbonate levels (< 18 mmol/L) were assigned to the DKA group. Standardized treatment was given according to current guidelines and hospital policy based on a low-dose insulin treatment regimen with the initial rate of 0.1 U/kg BW for every hour intravenously. If needed, the infusion dose was increased.

Exclusion criteria were as follows: age under 18 years; having obvious precipitating condition like infection, gastrointestinal bleeding, acute coronary syndromes, pregnancy, or chronic renal failure; and acute or chronic pancreatitis. Beyond laboratory findings, history and physical examination were used by emergency and ICU physicians to rule out acute infections.

Laboratory tests were performed via hospital laboratory. White blood cell (WBC) and platelet (Plt) counts, hemoglobin (Hgb), hematocrit (Htc), glucose, sodium, potassium, calcium, albumin, C-reactive protein levels, and blood gas parameters (pH , bicarbonate, pCO_2 , PO_2 , lactate) were recorded on the hospitalization day. Blood samples drawn at admission into pyrogen-free vacutainer tubes containing ethylenediaminetetraacetic acid (EDTA) and plasma were separated for cytokine analysis. Samples were stored at -80°C and thawed only one time.

Plasma IL-6, IL-1 β , and TNF- α concentrations were detected by enzyme-linked immunosorbent assay ELISA using the Invitrogen (Thermo Fisher Scientific, Waltham, MA, USA) kit and Biotek ELx800 (Biotek Inc., Winooski, VT, USA) analyzer. Normal values of TNF- α , IL-1 β , and IL-6 levels were 1.7 pg/mL, 1 pg/mL, and 2 pg/mL, respectively. The analyses and calibrations were performed according to the manufacturer's specifications.

Sample size

Power analysis was performed for a two-tailed exact test with the power of 80%, medium effect size (0.5), α error value with 0.05, and 29 subjects were needed for two groups.

Statistical analyses

For continuous variables, the mean $\pm$ standard deviation values were given. The Kolmogorov-Smirnov test was used to test the normal distribution of data. For comparison of continuous variables, the Students t-test and Mann-Whitney U test were used for normally and non-normally distributed data, respectively. A chi-square test was used to compare categorical values. Pearson correlation was used to measure the strength and direction of the relationship between the LOS and other parameters. Partial correlation was used to test the relationship between two variables while controlling for a third variable. All statistical tests were performed with the Predictive Analytics Software (PASW®, version 18, SPSS Inc., Chicago, IL).

RESULTS

A total of 74 patients (31 patients in the DKA group and 43 patients in the non-DKA (NDKA) group) were enrolled in the study. There was no difference between the two groups in terms of age, gender, LOS, Hgb, Htc, Plt, and lactate levels (Table 1). The DKA group showed higher serum glucose levels than the

non-DKA group ($p=0.013$).

IL-6, IL-1 β , and TNF- α levels did not show any difference between the DKA and NDKA groups ($p=0.784$, 0.413 , and 0.288 , respectively).

There was a negative correlation between LOS and pH (Pearson correlation= -0.25 ; $p=0.03$). Our data also showed a positive correlation between IL-6 levels and LOS time ($n=74$, Pearson correlation= 0.33 ; $p=0.004$) (Table 2). Partial correlation coefficients are given in Table 3 for IL-6 and LOS.

DISCUSSION

The main finding of this study is the association between IL-6 levels and LOS in hyperglycemic adult ICU patients. To the best of our knowledge this may be the first report on this specific topic.

Recently, Taniguchi *et al.* reported an

association between LOS and IL-6 in adult trauma patients. They assessed the IL-6 levels on ED arrival, and their findings supported that the prolonged length of ICU stay correlated with high IL-6 levels. They supported the hypothesis that determining blood IL-6 levels on arrival may be useful to predict the injury severity and outcomes in the early phase of trauma. They also reported a significant association between IL-6 levels and 28-day mortality rates (25). Our data showed similar results in hyperglycemic patients admitted to the ICU, and there was a positive association between IL-6 levels and LOS time. Therefore, baseline IL-6 levels may be a useful tool to predict the LOS and, potentially, the prognosis of hyperglycemic patients.

Siljan *et al.* reported an association between high IL-6 and IL-8 levels on admission and CURB-65 score. They also reported that short-term outcomes were associated with IL-6 levels (26). Moreover, in a study

Table 1. Demographics, laboratory results, and cytokine levels of patients on hospitalization day

Parameters	Groups	n	Mean $\pm$ SD (min.-max.)	CI 25%-75%	p
Sex (M/F)	NDKA	16/27	N/A	N/A	0.681*
	DKA	13/18			
Age (years)	NDKA	43	45.72 $\pm$ 16.41	-1.86–13.69	0.134**
	DKA	31	39.81 $\pm$ 16.78		
LOS (days)	NDKA	40	4.63 $\pm$ 4.55	-2.20–1.78	0.545***
	DKA	29	4.84 $\pm$ 3.78		
WBC ($10^3/\text{mm}^3$)	NDKA	40	4.49 $\pm$ 3.04	2.81–7.21	0.622***
	DKA	29	4.44 $\pm$ 4.79		
CRP (mg/dL)	NDKA	37	31.55 $\pm$ 91.88	5.95–19.52	0.547***
	DKA	28	65.53 $\pm$ 129.81		
Hgb (g/dL)	NDKA	43	13.32 $\pm$ 2.09	-1.07–0.94	0.891**
	DKA	31	13.39 $\pm$ 2.19		
Htc (%)	NDKA	43	40.54 $\pm$ 5.62	-3.69–1.92	0.532**
	DKA	31	41.42 $\pm$ 6.46		
Plt ($10^3/\text{mm}^3$)	NDKA	43	287.82 $\pm$ 114.04	-98.44–13.73	0.137**
	DKA	31	330.18 $\pm$ 126.54		
Lactate (mmol/L)	NDKA	43	2.33 $\pm$ 1.64	-0.18–1.15	0.148**
	DKA	31	1.84 $\pm$ 1.01		
Glucose (mg/dL)	NDKA	43	373.68 $\pm$ 132.14	-166.56–(-20.43)	0.013**
	DKA	31	467.17 $\pm$ 183.39		
pH	NDKA	43	7.31 $\pm$ 0.13	0.05–0.16	0.001**
	DKA	31	7.20 $\pm$ 0.10		
HCO ₃ (mmol/L)	NDKA	43	17.01 $\pm$ 3.32	3.49–7.19	0.001**
	DKA	31	11.67 $\pm$ 4.69		
Insulin (mIU/L)	NDKA	15	83.98 $\pm$ 228.56	8.25–55.86	0.523***
	DKA	10	46.32 $\pm$ 92.21		
IL-6 (pg/mL)	NDKA	43	30.58 $\pm$ 70.79	-49.41–26.69	0.784***
	DKA	31	41.89 $\pm$ 93.25		
IL-1 β (pg/mL)	NDKA	43	1.75 $\pm$ 3.92	-2.30–1.51	0.413***
	DKA	31	2.15 $\pm$ 4.24		
TNF- α (pg/mL)	NDKA	43	44.69 $\pm$ 49.55	-10.79–27.53	0.288***
	DKA	31	36.32 $\pm$ 23.56		

CI: Confidence interval, CRP: C-reactive protein, DKA: Diabetic ketoacidosis, HCO₃: Bicarbonate, Htc: Hematocrit, Hgb: Hemoglobin, IL: Interleukin, LOS: Length of stay, M/F: Male/Female, N/A: Non-applicable, NDKA: Non diabetic ketoacidosis, Plt: Platelet, SD: Standard deviation, TNF: Tumor necrosis factor, WBC: White blood cell count, *: Chi-Square test, **: Students t-test, ***: Mann-Whitney U test.

Table 2. Bivariate correlation values for hospitalization time and studied parameters

	Bivariate correlation coefficient	p*
Insulin (mIU/L)	0.020	0.919
pH	-0.244	0.036
Glucose (mg/dL)	0.032	0.784
WBC ($10^3/\text{mm}^3$)	-0.140	0.233
CRP (mg/dL)	0.222	0.064
Lactate (mmol/L)	-0.082	0.488
IL-6 (pg/mL)	0.330	0.004
IL-1 β (pg/mL)	0.080	0.495
TNF- α (pg/mL)	0.029	0.807

CRP: C-reactive protein, IL: Interleukin, TNF: Tumor necrosis factor, WBC: White blood cell count, *: Pearson correlation test.

Table 3. Partial correlation values to test the relationship between length of stay time and IL-6 levels while controlling for third variables

Control variable	Two-tailed partial correlation coefficient	p	Difference between correlation coefficients
Insulin (mIU/L)	0.791	0.000	0.471
pH	0.374	0.001	0.044
Glucose (mg/dL)	0.326	0.005	0.004
WBC ($10^3/\text{mm}^3$)	0.311	0.007	-0.019
CRP (mg/dL)	0.290	0.015	-0.04
Lactate (mmol/L)	0.337	0.004	0.007
IL-1 β (pg/mL)	0.327	0.005	0.003
TNF- α (pg/mL)	0.352	0.002	0.022

CRP: C-reactive protein, IL: Interleukin, TNF: Tumor necrosis factor, WBC: White blood cell count.

conducted by Mors *et al.* in trauma patients, it was shown that there was a significant increase in IL-6 levels in male trauma patients. They concluded that in male trauma patients, higher systemic IL-6 levels were associated with systemic inflammatory response syndrome (SIRS) and sepsis (27). We excluded infections, and the DKA and NDKA groups did not show any difference in terms of WBC and CRP levels. Therefore, our data were compatible with their findings, and higher IL-6 levels seem to be associated with longer ICU stay. Although we did not evaluate the prognosis of the patients, according to these data, one can say that IL-6 levels may be a good marker in the prediction of LOS and prognosis of traumatic and non-traumatic adult patients.

Bacci *et al.* reported a significant reduction of IL-6 levels in CAP patients seven days after hospitalization. Besides IL-6, they determined IL-1, TNF- α , CRP, and homocystein levels, and they stated that IL-6 and TNF- α levels were associated with early mortality of CAP patients. As an interesting finding of their study, CRP was not a good marker in the prediction of LOS and mortality compared to IL-6 (28). Wiryana *et al.* reported a significant decrease in IL-6 levels and events of SIRS in intensive insulin therapy compared to a conventional insulin regimen. However, these findings were not valid for TNF- α . Our findings were compatible with these studies, and as well pH levels, IL-6 may be a predictor of LOS. Conversely, CRP and TNF- α levels were not associated with LOS

in hyperglycemic patients with or without DKA.

Karavanaki *et al.* investigated the cytokine levels in pediatric DKA patients and found a significant increase in IL-6 levels. That increase was observed in severe and moderate DKA groups but not in the group with mild DKA. For that reason, they suggested that the persistence of increased IL-6 levels after treatment could be associated with the development of clinical brain or pulmonary edema in children with severe DKA (12). Our results did not show any difference between DKA and NDKA groups, which may be a result of the population difference between the two studies. Adult and children hyperglycemic patients may differ in proinflammatory response.

IL-6 levels were significantly lower after the intensive insulin treatment strategy than after the conventional insulin therapy, but this phenomenon was not valid for TNF- α (29). Our results showed that IL-6 levels were correlated with the LOS in adult hyperglycemic patients admitted to the ICU, and blood insulin levels were the strongest factor in this correlation. However, because the pre-admission treatment of the patients was not evaluated in this study, a definitive conclusion could not be made. Further evaluation of these findings, especially with newly diagnosed diabetics, might be beneficial.

Limitations

The following limitations should be considered.

First, our study was performed at a single hospital, thereby possibly limiting its generalizability. Second, repeated cytokine measurements were performed during hospital stay. Third, any outcome measure, such as 28-day mortality, was not defined.

In conclusion, blood IL-6 levels showed a positive correlation with the LOS in hyperglycemic ICU patients. These findings suggest the potential utility of the blood IL-6 level on admission as a predictive tool for LOS. On the basis of the literature review, further studies investigating the effect of IL-6 levels on glucose metabolism may be beneficial.

Conflict of interest

The authors declare that they have no conflict of interest.

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