Original Article

The effect of insulin resistance on mortality in critically ill patients in the intensive care unit

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Abstract

Background and Aims: Insulin resistance can be described as a subnormal biological response to a specific insulin concentration or deterioration of an accepted response to insulin in glucose homeostasis and deficiency of insulin response. The aim of this study is to evaluate the effect of insulin resistance on mortality in critically ill patients.

Methods: Over 18-year-old and nondiabetic 150 patients that had been hospitalized in an intensive care unit (ICU) between September 2013 and October 2014 were enrolled in this study. The Acute Physiology and Chronic Health Enquiry II (APACHE II), Glasgow Coma Scale, and Richmond Agitation and Sedation Scale were calculated on the day of admission to the ICU, and following 4th day and 1st, 2nd, 3rd, and 4th weeks. Insulin resistance was calculated using the HOMA formula. Infection and other complications during ICU stay, the requirement of mechanical ventilation (MV), nutritional status (parenteral and/or enteral), vasopressor, steroid, and insulin treatment were also recorded. Patients followed in the ICU were recorded as survivors and nonsurvivors.

Results: Glucose levels were found to be higher in nonsurvivor group at the 1st week and there was a significant positive relationship between APACHE II score and insulin resistance at the 3rd week. There was a significant relationship between mortality and requirement of MV, vasopressor medication, complications, and infection.

Conclusion: We conclude that the effect of insulin resistance seems to affect the mortality in critically ill patients after at least a 3 weeks long follow-up time.

Key Words: Acute Physiology and Chronic Health Enquiry II, homeostasis model assessment, insulin resistance, intensive care unit

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INTRODUCTION

Insulin resistance can be defined as a subnormal biological response to insulin at a given concentration or a deterioration in the expected effect of insulin on glucose homeostasis and a lack of response to insulin.[1] Metabolically, insulin resistance can be defined as a decrease in the effect of insulin on metabolic processes

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or a decrease in sensitivity to insulin at the cell level. Clinically, patients with insulin resistance should produce or utilize insulin at a level that exceeds the amount of insulin he has to release from the pancreas to maintain daily metabolic functions physiologically.[2] Insulin resistance is a common phenomenon in public health. Not only insulin resistance is common in individuals with type 2 diabetes mellitus and obesity but also the rate of insulin resistance among nonobese and people with normal glucose tolerance is approximately 25%.[3] Insulin sensitivity fluctuates over a wide range even in normal glucose-tolerant healthy individuals, and the prevalence of insulin resistance is not exactly known.[1] The HOMA (Homeostasis Model Assessment) is the most commonly used formula for the determination of insulin resistance. A HOMA value of 2.5 and above indicates insulin resistance; the greater the value, the greater the insulin resistance.

In recent years, it has been observed that insulin resistance is more common than expected in critically ill patients in the intensive care unit (ICU).[4] Due to the adverse effects of uncontrolled hyperglycemia on the cellular and metabolic level, it becomes detrimental in time and adversely affects the course of the critical disease. The duration of ICU stay was found to be longer in insulin-resistant patients in a study comparing the duration of ICU stay, intensive care mortality, infection development, and days of mechanical ventilation (MV) in patients who developed early insulin resistance and did not have insulin resistance. However, no significant difference was found in terms of mortality.[5] In a study, in which critical patients in the ICU with hyperglycemia were observed, the mortality was significantly decreased in patients receiving intensive insulin therapy compared to those receiving conventional therapy.[6] In this study, we investigated the relationship between the HOMA index, an indicator of insulin resistance, and mortality in nondiabetic critically ill patients in the ICU. Furthermore, the relation of the Acute Physiology and Chronic Health Enquiry II (APACHE II), Glasgow Coma Scale (GCS), Richmond Agitation and Sedation Scale (RASS) scoring and medication, nutritional status, and ventilation status with mortality were investigated.

METHODS

Our study included 150 nondiabetic patients aged over 18 years those hospitalized in a University Hospital ICU, Department of Anesthesiology and Reanimation between September 2013 and October 2014. Since stress hyperglycemia may also occur during hospitalization, it was determined whether the patient in the intensive care had diabetes and confirming if he was taking diabetes medication. The ethical approval was obtained from Ethics Committee dated September 14, 2013. Patients under 18 years of age, patients with diabetes mellitus, pregnant women, and those with intensive care hospitalization shorter than 48 h were excluded from the study. Age, sex, weight, height, BMI (Body Mass Index), and diagnosis of the patients at hospitalization were recorded. Blood glucose levels and other biochemical parameters were recorded on the day of admission to the ICU, and following 4^{th} day and 1^{st}, 2^{nd}, 3^{rd} and 4^{th} weeks. In addition, APACHE II, GCS and RASS scores were also calculated and recorded on the above-mentioned days. Insulin in serum was analyzed using ADVIA Centaur CP System; (Siemens Health-care Diagnostics). Blood glucose was analyzed using a Beckman Coulter LH 680 Hematology Analyzer (Florida, USA). Correlations between the calculated insulin resistance values, and the scorings and the effect of this on mortality were investigated. The HOMA (Homeostasis Model Assessment) formula was used to calculate insulin resistance.[7]

HOMA = G_a (×) I_a/22.5 (G_a: Fasting plasma glucose concentration [mM/L], I_a: Fasting plasma insulin concentration [plasma U/L]).

The HOMA test value of 2.5 and above is considered as insulin resistance. Infection (lower respiratory tract infections, i.e., acute bronchiolitis, urinary tract infection, decubitus infection, soft-tissue infection, and osteomyelitis) and complications (acute or chronic cerebral diseases, acute or chronic pulmonary pathologies, chronic organ failure, and neuromuscular diseases, etc.) were recorded during the follow-up period of the patients in the ICU. MV requirement, nutritional status (parenteral and/or enteral), vasopressor, steroid, and insulin treatments were recorded and their relationship with mortality were evaluated.

We made the statistical analysis of data by SPSS (Version 21.0) (SPSS Inc, Chicago, IL, USA) package program. In this prospective study, in addition to descriptive statistics, chi-square test was used for nominal data and student test was used for numerical data. ANOVA was used in the comparison of repeated measurements in a group; paired *t*-test was used if the result was significant in this test. Pearson's correlation coefficient analysis was also used. Receiver-operating characteristic (ROC) analysis was used. We used multiple logistic regressions to determine factors predicting the mortality of patients in ICU. In all tests, $P < 0.05$ was considered statistically significant.

RESULTS

Table 1 shows the comparison of the demographic characteristics of patients according to the outcome. The mean age of the patients was 64.26 ± 19.84 (18–98) years. About 66.5% of the cases were male (n = 103) and 33.5% were female (n = 52). Among the 155 hospitalized patients, 88 were medical and 67 were surgical critically ill patients. The mean duration of ICU stay was 67 days (4–375 days). Renal replacement therapy was applied to 33 patients and 25 of them had no history of renal dysfunction. Sixty-seven patients died in the ICU and 88 of them survived. The mean age of nonsurvivor group (67.9 ± 19.4) was higher than the mean age of the patients survivor group (61.5 ± 19.8) (P = 0.045). There was no significant difference in weight, height, and BMI variables between the two groups. Table 2 shows comparison of HOMA, Glasgow, APACHE II, and RASS values of both groups. Blood glucose levels were found to be higher in nonsurvivor group at the 1st week. HOMA values measured during a month period did not differ significantly between the two groups. Apache II scores of nonsurvivor group were significantly higher compared to those survivor group; on the 1st day (23.1 ± 8.6 vs. 12.1 ± 6.2) (P = 0.000), 4th day (23.3 ± 9.6 vs. 10.7 ± 5.8) (P = 0.000), 1st week (21.8 ± 6.2 vs. 11.5 ± 5.0) (P = 0.000), and 2nd week (22.0 ± 1.7 vs. 15 ± 2.5) (P = 0.029) of hospitalization. The GCS values of nonsurvivor group were significantly lower than those survivor group on the 1st day (8.4 ± 4.2 vs. 13.3 ± 3.4) (P = 0.000), and the 4th day (8.3 ± 3.9 vs. 13.9 ± 2.4) (P = 0.000), 1st week (7.5 ± 4.0 vs. 13.6 ± 2.4) (P = 0.000), and 2nd week (8.1 ± 0.8 vs. 12 0 ± 0.9) (P = 0.011) of hospitalization. The mean of RASS scores of nonsurvivor group were significantly lower than those survivor group on the 1st day (−2.0 ± 2.4 vs. 0.5 ± 1.6), the 4th day (−1.8 ± 2.5 vs. 0.7 ± 1.3), and 1st week (−2.2 ± 2.6 vs. 1.0 ± 1.2) (all P = 0.000).

There was a positive correlation between APACHE II and HOMA only on the 3rd week (r = 0.623, P < 0.002). No statistically significant value was found in the ROC curve analysis to determine a cutoff value for HOMA and APACHE II values (for death in ICU = 1) [Table 3 and Figure 1].

The complication rate [Figure 2] (73% vs. 35%), and the rate of infection (81% vs. 65%) was significantly higher nonsurvivor group compared to the survivor group. While 93% of nonsurvivor group had MV support, this rate was 59% for the survivor group. It is seen that 28% and 2% of the nonsurvivor group and of the survivor group, respectively, did not receive any nutritional support (enteral or parenteral). About 51% of nonsurvivor group took vasopressor and 25% of them took insulin therapy, while the rates for survivor group were 6% and 1.1%, respectively [Table 4].

Table 1: Comparison of demographic characteristics of patients according to outcome

	Mean±SD (n)		P
	Survivor group	Nonsurvivor group	
Age (years)	61.5±19.8 (88)	67.9±19.4 (67)	0.045
Weight (kg)	72.8±12.3 (88)	73.3±19.5 (67)	0.848
Height (cm)	166.4±8.6 (88)	166.1±8.4 (67)	0.839
BMI	26.4±4.9 (88)	26.7±7.9 (67)	0.810

SD: Standard deviation, BMI: Body mass index

Table 2: Comparison of Homeostasis Model Assessment, Glasgow, Acute Physiology and Chronic Health Enquiry II and Richmond Agitation and Sedation Scale values on the first, 4th, 7th, 14th, 21st, and 28th days of intensive care unit

	Mean±SD (n)		P
	Survivor group	Nonsurvivor group	
Glucose			
1st day	127.5±41.3 (88)	134±65.1 (68)	0.468
4th day	119.1±37 (75)	126.6±47.8 (55)	0.314
1st week	93.2±34.7 (23)	143.9±46 (35)	0.001
2nd week	104.6±8.7 (8)	141.5±29.8 (23)	0.571
3rd week	129.8±18.5 (4)	138.7±16.4 (18)	0.952
4th week	91.8±4.3 (4)	125.6±10.3 (15)	0.088
HOMA			
1st day	1.2±1.0 (88)	1.5±2.4 (68)	0.256
4th day	1.2±1.3 (75)	1.4±3.1 (55)	0.707
1st week	1.3±1.1 (23)	1.5±2.2 (35)	0.713
2nd week	0.9±0.3 (8)	1.0±0.2 (23)	1.000
3rd week	0.9±0.6 (4)	0.9±0.2 (18)	0.733
4th week	0.4±0.1 (4)	2.8±1.5 (15)	0.110
Glasgow			
1st day	13.3±3.4 (88)	8.4±4.1 (68)	0.000
4th day	13.9±2.4 (75)	8.3±3.9 (56)	0.000
1st week	13.6±2.4 (24)	7.5±4.0 (36)	0.000
2nd week	12.0±0.9 (8)	8.1±0.8 (24)	0.011
3rd week	10.8±1.9 (4)	8.4±0.8 (18)	0.298
4th week	11.3±1.8 (4)	7.5±0.8 (15)	0.078
APACHE			
1st day	12.1±6.2 (88)	23.1±8.6 (67)	0.000
4th day	10.7±5.8 (75)	23.3±9.6 (55)	0.000
1st week	11.5±5.0 (24)	21.8±6.2 (36)	0.000
2nd week	15.0±2.5 (8)	22.0±1.7 (24)	0.029
3rd week	23.0±4.5 (4)	22.3±1.7 (18)	0.391
4th week	19.3±3.9 (4)	21.5±1.8 (15)	0.615
RASS			
1st day	0.5±1.6 (88)	−2.0±2.4 (67)	0.000
4th day	0.7±1.3 (75)	−1.8±2.5 (55)	0.000
1st week	1.0±1.2 (24)	−2.2±2.6 (36)	0.000
2nd week	0.4±0.5 (8)	−1.9±0.6 (24)	0.062
3rd week	−1.0±1.2 (4)	−1.9±0.6 (18)	0.365
4th week	−1.0±0.9 (4)	−2.7±0.6 (15)	0.169

HOMA: Homeostasis Model Assessment, APACHE II: Acute Physiology and Chronic Health Enquiry II, RASS: Richmond Agitation and Sedation Scale, SD: Standard deviation

Multiple logistic regression analysis showed that there was a significant relation between mortality and insulin medication (odds ratio [OR], 34,729: 95% confidence interval [CI], 2389–504,842), vasopressor medication (OR, 6934: 95% CI, 2177–22,082), mechanical ventilation support (OR, 3402: 95% CI, 928–12,474), complication (OR, 3220: 95% CI, 1313–7896), and infection (OR, 2182: 95% CI, 652–7302) [Table 5].

DISCUSSION

The results of this study showed blood glucose levels were found to be higher in nonsurvivor group at the 1st week, and there was a significant positive relationship between APACHE II score and insulin resistance at the 3rd week in patients who were monitored in the ICU for about 1 month. Besides, APACHE II scores of nonsurvivor group were higher than survivor group, whereas GCS and RASS values were lower. Nonsurvivor group in the intensive care period developed more complications, infections, and needed more MV support. While these patients had higher rates of vasopressor drug, insulin therapy, and less nutritional support.

The risk of mortality and serious morbidity is higher in critically ill patients who stay longer than 5 days in ICU. These patients have a high risk of sepsis, increased inflammation, critical disease polyneuropathy, and then these factors can cause death. Intensive care patients develop hyperglycemia and insulin resistance, even if they do not already have diabetes. It has been reported that hyperglycemia is not a useful adaptation in intensive care patients and increases the duration and mortality in ICU.[8,9]

Van den Berghe compared intensive care patients who received intensive insulin therapy and conventional insulin therapy. The mortality rate was reduced by 40% in the intensive insulin therapy group and in the conventional treatment group whose blood glucose level were between 80 and 200 mg/dl, mortality rate decreased from 20.2% to 10.6%.[10] In a retrospective study of patients in surgical and medical ICU by Gabbanelli *et al*., the relationship between mortality and hyperglycemia was investigated and blood glucose levels of 141.7 mg/dL were shown to have a sensitivity of 76% and a specificity of 56.5% to differentiate the probability of death.[11] In this study, we observed that in the ICU follow-up period of 28 days, only blood glucose values in the 1st week were higher in the nonsurvival group than the survival group; however, there was no difference between the two groups in the other

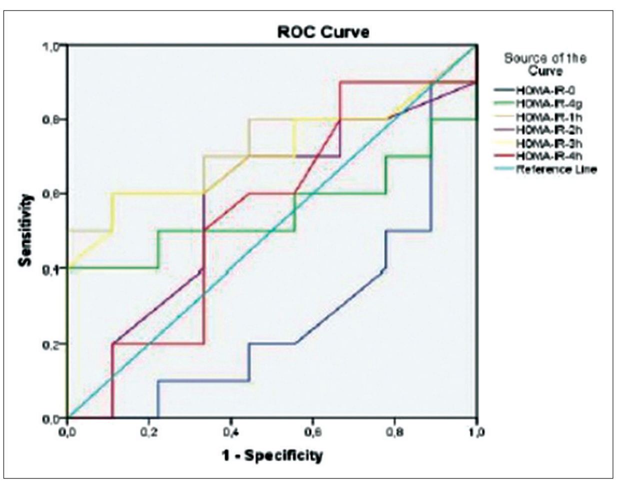

Figure 1: Receiver operating characteristic curve graphics for HOMA values. HOMA: Homeostasis Model Assessment

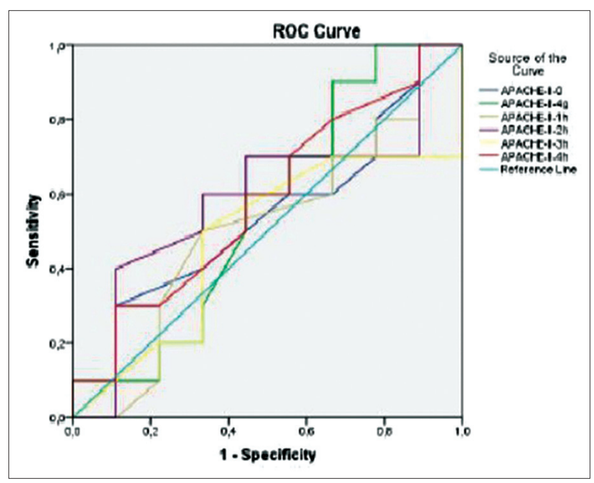

Figure 2: Receiver operating characteristic curve graphics for APACHE II values. APACHE: Acute Physiology and Chronic Health Evaluation

Table 3: Correlation between Homeostasis Model Assessment and Acute Physiology and Chronic Health Enquiry II

	APACHE-1st day (r, P)	APACHE-4th day (r, P)	APACHE-1st week (r, P)	APACHE-2nd week (r, P)	APACHE-3rd week (r, P)	APACHE-4th week (r, P)
HOMA-1st day	0.016, 0.843	-	-	-	-	-
HOMA-4th day		0.019, 0.831	-	-	-	-
HOMA-1st week	-	-	−0.049, 0.831	-	-	-
HOMA-2nd week	-	-	-	0.118, 0.520	-	-
HOMA-3rd week	-	-	-	-	0.623, 0.002	-
HOMA-4th week	-	-	-	-	-	0.014, 0.954

HOMA: Homeostasis Model Assessment, APACHE II: Acute Physiology and Chronic Health Enquiry II

Table 4: Comparison of patients by means of complication, infection, mechanical ventilation support, nutritional status, inotropic treatment, steroid treatment, and insulin therapy according to outcome

	Survivor group, *n* (%)	Nonsurvivor group, *n* (%)	*P*
Complication*			
Yes	47 (73.4)	32 (35.2)	0.000**
No	17 (26.6)	59 (64.8)	
Infection**			
Yes	52 (81.2)	60 (65.9)	0.036*
No	12 (18.8)	31 (34.1)	
Mechanical ventilation support			
Yes	60 (93.8)	54 (59.3)	0.000**
No	4 (6.2)	37 (40.7)	
Nutrition			
No	18 (28.1)	2 (2.2)	0.000**
Enteral	21 (32.8)	72 (79.1)	
Parenteral	3 (4.7)	1 (1.1)	
Enteral + parenteral	22 (34.4)	16 (17.6)	
Inotropic medication			
Yes	33 (51.6)	6 (6.6)	0.000*
No	31 (48.4)	85 (93.4)	
Steroid medication			
Yes	29 (45.3)	37 (40.7)	0.564
No	35 (54.7)	54 (59.3)	
Insulin medication			
Yes	16 (25.0)	1 (1.1)	0.000**
No	48 (75.0)	90 (98.9)	

*Complication: Acute or chronic cerebral diseases, acute or chronic pulmonary pathologies, chronic organ failure, neuromuscular diseases, etc., **Infection: Lower respiratory tract infections (i.e., acute bronchiolitis), urinary tract infection, decubitus infection, soft-tissue infection, osteomyelitis

Table 5: Logistic regression analysis* of factors predicting the mortality of patients in intensive care unit

Independent variables	OR	95% CI	*P*
Complication	3.220	1.313-7.896	0.011
Infection	2.182	0.652-7.302	0.205
Mechanical ventilation support	3.402	0.928-12.474	0.065
Nutrition	0.024	0.003-0.221	0.001
Vasopressor medication	6.934	2.177-22.082	0.001
Steroid medication	0.692	0.267-1.795	0.449
Insulin medication	34.729	2.389-504.842	0.009

*Nagelkerge R^2=0.586. Hosmer–Lemeshow test P=0.944. OR: Odds ratio, CI: Confidence interval

measurements. We aimed to keep blood glucose levels in the 140–180 range by increasing the frequency of blood glucose monitoring in patients with high glucose levels monitored in the ICU and with insulin therapy.

In a meta-analysis of the effect of insulin therapy on mortality in patients in the surgical ICU with critical disease, Pittas *et al*. found that short-term mortality was reduced by 15% in diabetic patients taking insulin therapy who had myocardial infarction and not treated with reperfusion therapy.[12] Finney *et al*. investigated the role of insulin dose and glycemic control in decrease in mortality by insulin therapy and stated that glycemic control had an effect rather than the amount of exogenous insulin in the decrease in mortality[12] In a meta-analysis of the benefits and risk of strict blood glucose control, a significant reduction in the risk of sepsis was demonstrated in patients hospitalized in surgical intensive care rather than medical intensive care patients.[13] However, there are also studies showing that intensive insulin therapy is not effective on mortality in surgical and medical-critical patients.[14-16]

Considering the debate on optimal blood glucose targets in ICU, it is reasonable to aim at keeping blood glucose levels at around 140 mg/dl, which seems reasonable to prevent hypoglycemia attacks and minimize glycemic variability. Using computer-based algorithms, the ideal insulin titration can be performed with insulin infusion systems and ideal glycemic control can be achieved. Similarly, arterial and venous blood samples should be taken instead of measuring by the finger stick, and the monitoring technology should be available. In parallel, appropriate staff and enteral nutritional support are also required. As a result, there should be an appropriate protocol for the prevention and treatment of hypoglycemia attacks.[6]

The APACHE II is a scoring system used to determine the severity of the disease in ICU patients. The high APACHE II score measured in the first 24 h was associated with the mortality risk of ICU.[17,18] Consistent with this, in the present study, APACHE II scores, which were measured on the 1st day of admission in the ICU were significantly higher in nonsurvival group than survivor group. In a study in which APACHE III was used to determine the severity of disease in ICU, no correlation was found between insulin resistance and APACHE III score.[19] In our study, there was a significant positive correlation between APACHE II score and insulin resistance at the 3rd week. Despite the insulin resistance in the first 2 weeks, the mortality scoring measurements did not increase; the increase observed in mortality at the 3rd week was associated with delayed cellular and systemic changes caused by insulin resistance. However, it was thought that the process accelerated due to the presence of other comorbid pathologies in our patients. Since our patient follow-up was limited to 4 weeks, it suggested that insulin resistance and its effect on mortality could be a short process.

CONCLUSION

There was a correlation between insulin resistance and mortality only at 3 weeks. A longer follow-up might establish a strong relationship between insulin resistance and mortality.

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Conflicts of interest

There are no conflicts of interest.

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