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Glucose intolerance in intensive care patients: Incidence and outcome

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ABSTRACT

Background: Critical illness is associated with modification in metabolic status. Insulin resistance and elevated blood glucose levels occur during stressful conditions. We aimed to evaluate the incidence and outcome of glucose intolerance in intensive care patients.

Material and methods: This prospective clinical study included 290 patients, admitted to the intensive care unit (ICU). They were divided into three groups according to the maximum blood glucose level on admission and after 48 hours of admission: Normoglycemic, hyperglycemic, and hypoglycemic. Each group was subdivided into diabetic and non-diabetic. Patients' age, sex, APACHE II, and causes of admission were recorded. Use of vasopressor and corticosteroid therapy, type of feeding, days on mechanical ventilation, total days of stay in ICU, and fate of patients were recorded.

Results: Hyperglycemia was common in critically ill patients with 68.6% and 86.2% incidence on ICU admission and after 48 hours of admission, respectively. Sixty percent of the patients were diabetic. Hyperglycemia was associated with increased morbidity in the form of difficult weaning from mechanical ventilation and long ICU stay. Of hyperglycemic patients, 66.4% were orally fed. The mortality incidence among normoglycemic patients was 37.5%; which was lower than the mortality among hyperglycemic patients (39.2%), but without a statistically significant difference. Glucose intolerance was not related to the severity of the disease or cause of admission. Vasopressors and steroids were not risking factors during the initial 48 hours of admission.

Conclusion: Glucose intolerance is high in intensive care patients and is associated with high morbidity and mortality.

1. Introduction

Glucose homeostasis is important for cellular function. Several hormones are involved in glucose metabolism and maintenance of normoglycemia, which reflects the balance between the ability to stimulate glucose disposal and simultaneously suppress endogenous glucose production. This is determined by three factors: insulin sensitivity, glucose effectiveness, and insulin secretion [1]. Various organs contribute to glucose metabolism, and body metabolism is adapted during fasting to decrease global glucose disposal [2].

Critical illness activates the hypothalamic-pituitary-adrenal axis, resulting in the release of cortisol, which stimulates gluconeogenesis and decreases glucose utilization. Other hormones (glucagon, catecholamines, and growth hormone) are also released and stimulate insulin resistance through lipolysis of adipose tissue, skeletal muscle proteolysis, and hepatic gluconeogenesis. These processes impair glucose utilization in peripheral tissues, increase circulating free fatty acids, and stimulate gluconeogenesis and glycogenolysis. Exogenous factors (parenteral and enteral nutrition, vasopressors, glucose infusions, and corticosteroids) exacerbate hyperglycemia [3].

Glucose intolerance frequently occurs in the critically ill, in both diabetics, and those who were previously glucose-tolerant. The term "stress hyperglycemia" reflects the pathogenesis of the latter group [4]. Stress hyperglycemia is defined as an increase in blood glucose above 200 mg/dl in presence of acute illness, without previously diagnosed diabetes [3].

The target blood glucose level in the Intensive Care Unit (ICU) is recommended to be from 140 to 180 mg/dl, not tight control (80–110 mg/dl) or liberal range (180–200 mg/dl) [5]. Blood glucose value for hyperglycemia differs in studies [6]. A plasma glucose concentration <70 mg/dl is the most common threshold used to define hypoglycemia. In critically ill patients, the diagnosis of hypoglycemia seems to be a challenge as glucose analyzers are habitually not consistent at the low ranges of blood glucose, and hypoglycemia-related neurological signs may be masked. More important, hypoglycemia in critical illness, especially severe hypoglycemia, is associated with a poor prognosis without clear identification of the reason for this higher mortality [7].

This research aimed to evaluate the incidence and outcome of glucose intolerance in intensive care patients.

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2. Material and methods

After approval of the faculty ethical committee, we conducted this prospective observational study on 290 critically ill patients, admitted to ICU to evaluate random blood glucose concentration on ICU admission, in addition to peak glucose concentration (defined acute hyperglycemia) on initial 48 hours of ICU admission. The study was conducted in both EL-Zaitoun and Sidnawy health insurance hospitals, Cairo, Egypt. The study included patients admitted to ICU, from December 2018 to January 2020. Written informed consent was taken from patients or their legal guardians.

We included patients with symptoms of acute illness and decided to be admitted to ICU as assessed by the Modified Early Warning Score (MEWS) algorithm. Patients were more than 18 years old and the period of stay in ICU for more than 24 hours. Patients less than 18 years old, stay period less than 24 hours, and patients with relative's refusal were excluded.

Patients involved in the study were divided into three groups according to the highest blood glucose level on admission and during the initial 48 hours of admission into normoglycemic, hyperglycemic, and hypoglycemic. Each group was subdivided into diabetic and non-diabetic. The following data were obtained: age, gender, APACHE II score, admission diagnosis, blood glucose level every 6 h. The highest blood glucose level during the first 48 hours of admission more than 140 mg/dl was used to define acute hyperglycemia; with mild hyperglycemia 140–180 mg/dL, moderate hyperglycemia 180–200 mg/dL, and severe hyperglycemia >200 mg/dL. Vasopressor and corticosteroid therapy, type of feeding, days on mechanical ventilation, total days of ICU stay, and outcome of patients were also recorded. Insulin infusion was ordered for patients of diabetic ketoacidosis (DKA) otherwise subcutaneously according to a sliding scale every 6 h. All these data were collected and compared between the three groups of patients.

2.1. Sample size justification

Sample size justification was calculated using MedCalc® version 12.3.0.0 program "Ostend, Belgium" statistical calculator based on 95% confidence interval and power of the study 80% with α error 5%. According to a previous study (Godinjak et al., 2015) [8], the overall prevalence of patients with hyperglycemia was 54% (35% with diabetes mellitus and 19% with stress hyperglycemia), while the mean of glycemic variability (mmol/l) in diabetes mellitus 7.5 versus stress-hyperglycemia 9.3, with significant p-value (<0.05). Also, outcome mortality in diabetes mellitus was 17 (48.6%) versus 10 (52.6%) in stress-hyperglycemia, with stress-hyperglycemia p-value (<0.05) significant. Again, recovery in diabetes mellitus was 18 (51.4%) versus 9 (47.4%) in stress-hyperglycemia, with significant p-value

(<0.05). So, it can be relied upon in this study. The sample size calculated according to these values produced a minimal sample size of 276 cases to find this difference. Assuming a drop-out ratio of 5%, the sample size was 290 cases.

2.2. Statistical analysis

IBM SPSS statistics (V. 26.0, IBM Corp., USA, 2019) was used for data analysis. Data were expressed as median and percentiles for quantitative nonparametric measures and both number and percentage for categorized data. The following tests were done:

(1) Comparison between two independent groups for non-parametric data using the Wilcoxon Rank Sum test.
(2) Comparison between more than 2 patient groups for non-parametric data using the Kruskal Wallis test.
(3) Chi-square test to study the association between every two variables or comparison between two independent groups as regards the categorized data. The probability of error at 0.05 was considered significant, while at 0.01 and 0.001 are highly sig.

3. Results

This prospective observational clinical study included 290 critically ill patients. On admission, our study revealed that 83 patients (28.6%) were normoglycemic while the remaining 207 patients (71.4%) showed glucose intolerance on ICU admission most of them were hyperglycemic (199 patients representing 68.6%) while the remaining were hypoglycemic (8 patients representing 2.8%). The hyperglycemic group on admission was subdivided into mild, moderate, and severe groups representing 55 patients, 12 patients, and 132 patients, respectively (Figure 1).

After 48 hours of admission and according to the peak of glucose level, the eight hypoglycemic patients on admission became hyperglycemic (Induced hyperglycemia). Also, some cases from the normoglycemic patients and mild hyperglycemic patients on admission developed either moderate or severe hyperglycemia. So, after 48 hours of admission, normoglycemic patients became 32 patients (11%) while the hyperglycemic patients became 250 patients (Figure 1). Forty-seven patients were non-diabetic and showed severe hyperglycemia representing stress hyperglycemia (Table 1).

Overall, 199 were males while 91 were females showing no statistically significant difference between the different study groups either on admission or after 48 hours of admission with P-value = 0.764 and 0.690, respectively. The diabetic patients represented 60% of the patients, while the rest 40% of the involved patients were non-diabetic. About the factors that
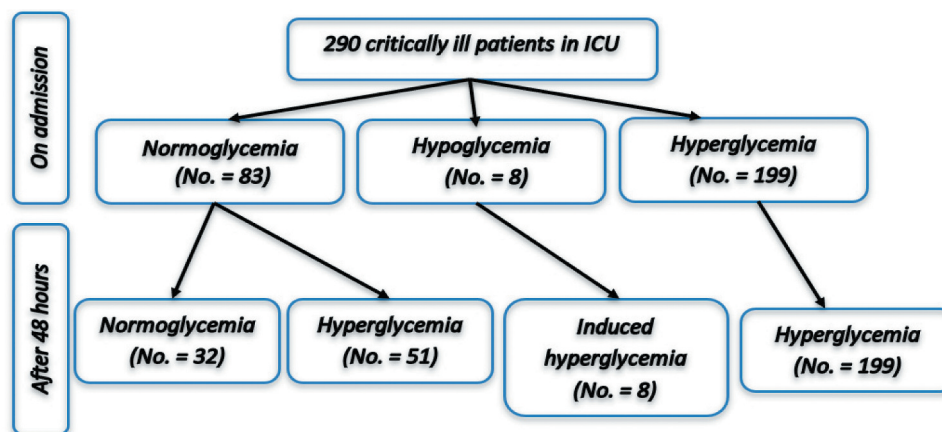
Figure 1. A flowchart of the study population.

Table 1. Distribution of known diabetic and non-diabetic patients involved in the study according to the glucose level on admission and the peak glucose level at 48 h of admission.

History of DM	Glucose level on admission					
	Hypoglycemia	Normoglycemia	Hyperglycemia			Total
			Mild	Moderate	Severe	
DM	4 (50%)	26 (31.3%)	23 (41.8%)	9 (75%)	112 (84.8%)	174 (60%)
Non-DM	4 (50%)	57 (68.7%)	32 (58.2%)	3 (25%)	20 (15.2%)	116 (40%)
Pearson Chi-square	Value = 71.429 P-value = 0.000					
	Peak glucose level on 48 h of admission					
	Induced hyperglycemia	Normoglycemia	Hyperglycemia			Total
			Mild	Moderate	Severe	
DM	4 (50%)	7 (21.9%)	9 (27.3%)	6 (27.3%)	148 (57.9%)	174 (60%)
Non-DM	4 (50%)	25 (78.1%)	24 (72.7%)	16 (72.7%)	47 (24.1%)	116 (40%)
Pearson Chi-square	Value = 64.793 P-value = 0.000					

may be associated with glucose intolerance on ICU admission or after 48 hours, our results revealed that diabetes showed a statistically significant correlation with glucose intolerance (Table 1). Forty-five patients needed insulin infusion as they suffered from Diabetic Keto Acidosis (DKA), 213 patients needed insulin subcutaneous according to the sliding scale and only 32 patients did not use insulin ever.

No significant statistical relation was found between glucose intolerance on admission or peak glucose level during 48 hours and age or APACHE II score (Tables 2 and 3). Also, no statistically significant difference was found between different groups as regards the smoking history and the cause of admission.

There was no significant correlation between glucose intolerance and the days of mechanical ventilation or days of stay in the ICU (Tables 2 and 3). But, moderate hyperglycemia on admission (180–200 mg/dl) was associated with a significantly prolonged stay on mechanical ventilation in comparison to normoglycemic, mild hyperglycemic (140–180 mg/dl), and sever hyperglycemic (>200 mg/dl) patients on admission (Table 2). According to the peak of glucose level on 48 h of admission, moderate and severe hyperglycemia was related to significantly prolonged stay in ICU in comparison to the normoglycemic group (Table 3).

A statistically significant difference was found between the type of feeding among our study groups with oral fed patients were the commonest. 166 patients of the total of 250 hyperglycemic patients (i.e., 66.4%) were orally fed (Table 4).

Regarding mortality, no statistically significant difference was found between the mortality and the glucose level on admission or at 48 hours. However, on admission or after 48 hours, the highest mortality incidence was found among moderate hyperglycemic patients (66.7% and 54.5%, respectively) (Table 5).

4. Discussion

Our study was carried out randomly on 290 patients admitted to ICU from December 2018 to January 2020. Patients were already diagnosed as having a critical illness of various causes. There is no standard blood glucose value for hyperglycemia [6]. Hence, in our study, we considered hyperglycemia >140 mg/dl. It was classified by the American Diabetes Association 2009 as mild hyperglycemia 140–180 mg/dL, moderate hyperglycemia 180–200 mg/dL, and severe hyperglycemia >200 mg/dL [5]. In our study, patients who developed hyperglycemia during the initial 48 hours of admission

Table 2. Kruskal–Wallis test and Wilcoxon rank-sum test for comparison between different groups of glucose intolerance on admission with age, APACHE II score and days of mechanical ventilation and ICU stay.

Glucose intolerance on admission		n	Median (year)	25 Perc	75 Perc	H	Wilcoxon rank-sum P-value	Sig.
Age (year)								
Hypoglycemia		8	65	58	67.75		0.549 (normo/moderate)	NS
Normoglycemia		83	68	58	74		0.737 (mild/moderate)	NS
Hyperglycemia	Mild	55	67	63	73		0.391 (moderate/severe)	NS
	Moderate	12	68	62	76.5			NS
	Severe	132	66	60	71.75			
Kruskal–Wallis test P						2.35	0.672	NS
APACHE II		*n*	*Median*	*25 Perc*	*75 Perc*	*H*	*Wilcoxon rank-sum P-value*	*Sig.*
Hypoglycemia		8	22.5	13.75	26.5		0.376 (normo/moderate)	NS
Normoglycemia		83	18	12	24		0.152 (mild/moderate)	NS
Hyperglycemia	Mild	55	15	12	23		0.162 (moderate/severe)	NS
	Moderate	12	22.5	11.75	30			NS
	Severe	132	17	10	23			
Kruskal–Wallis test P						4.83	0.305	NS
Day on MV		*n*	*Median*	*25 Perc*	*75 Perc*	*H*	*Wilcoxon rank -sum P-value*	*Sig.*
Hypoglycemia		8	0.5	0	2.125		0.019 (normo/moderate)	S
Normoglycemia		83	0	0	1		0.003 (mild/moderate)	HS
Hyperglycemia	Mild	55	0	0	0		0.016 (moderate/severe)	S
	Moderate	12	2	0	3.9375			
	Severe	132	0	0	1			
Kruskal–Wallis Test P						9.29	0.054	NS
ICU days		*n*	*Median*	*25 Perc*	*75 Perc*	*H*	*Wilcoxon rank-sum P-value*	*Sig.*
Hypoglycemia		8	4.5	1.8125	5.375		0.736 (normo/moderate)	NS
Normoglycemia		83	4	2.25	6.5		0.743 (mild/moderate)	NS
Hyperglycemia	Mild	55	4.25	2	6.25		0.962 (moderate/severe)	NS
	Moderate	12	4.25	2.1875	6.9375			NS
	Severe	132	4.25	2.3125	6.75			
Kruskal–Wallis test P						0.485	0.975	NS

Table 3. Kruskal–Wallis test and Wilcoxon rank-sum test for comparison between different groups of glucose intolerance on peak glucose level during 48 h of admission with age, APACHE II score, days of mechanical ventilation, days of ICU stay, days on steroid, and days on circulatory support.

	Glucose intolerance on 48 h		n	Median (year)	25 Perc	75 Perc	H	Wilcoxon rank-sum P-value	Sig.
Age (year)	Induced hyperglycemia		8	65	58	67.75			
	Normoglycemia		32	69.5	55.75	74.75		0.812 (normo/moderate)	NS
	Hyperglycemia	Mild	33	68	57	72.5		0.711 (normo/severe)	NS
		Moderate	22	66	58	73.5			
		Severe	195	66	61	72			
Kruskal–Wallis test P							1.096	0.895	NS
			n	Median	25 Perc	75 Perc	H	Wilcoxon rank-sum P-value	Sig.
APACHE II	Induced hyperglycemia		8	22.5	13.75	26.5			
	Normoglycemia		32	18	11	22		0.124 (normo/moderate)	NS
	Hyperglycemia	Mild	33	16	11.5	26		0.999 (normo/severe)	NS
		Moderate	22	21	13	28.5			
		Severe	195	17	11	23			
Kruskal– Wallis test P							3.858	0.426	NS
			N	Median	25 Perc	75 Perc	H	Wilcoxon rank-sum P-value	Sig.
Day on MV	Induced hyperglycemia		8	0.5	0	2.125			
	Normoglycemia		32	0	0	1		0.088 (normo/moderate)	NS
	Hyperglycemia	Mild	33	0	0	1		0.358 (normo/severe)	NS
		Moderate	22	0	0	4.4375			
		Severe	195	0	0	1.25			
Kruskal–Wallis test P							3.422	0.49	NS
			N	Median	25 Perc	75 Perc	H	Wilcoxon rank-sum P-value	Sig.
ICU days	Induced hyperglycemia		8	4.5	1.8125	5.375			
	Normoglycemia		32	3	1.5625	5.25		0.039 (normo/moderate)	S
	Hyperglycemia	Mild	33	3.5	1.375	7.75		0.012 (normo/severe)	S
		Moderate	22	4.75	2.5	7.875			
		Severe	195	4.25	2.5	6.75			
Kruskal–Wallis test P							7.238	0.124	NS
			N	Median	25 Perc	75 Perc	H	Wilcoxon rank-sum P-value	Sig.
Days on steroid	Induced hyperglycemia		8	0	0	0			
	Normoglycemia		32	0	0	0		0.298 (normo/moderate)	NS
	Hyperglycemia	Mild	33	0	0	0		0.233 (normo/severe)	NS
		Moderate	22	0	0	0			
		Severe	195	0	0	0			
Kruskal–Wallis test P							1.996	0.736	NS
			N	Median	25 Perc	75 Perc	H	Wilcoxon rank-sum P-value	Sig.
Days on circulatory support	Induced hyperglycemia		8	0	0	0.75			
	Normoglycemia		32	0	0	1		0.129 (normo/moderate)	NS
	Hyperglycemia	Mild	33	0	0	1		0.916 (normo/severe)	NS
		Moderate	22	0	0	5			
		Severe	195	0	0	1			
Kruskal–Wallis test P							4.568	0.335	NS

Table 4. Distribution of patients involved in the study according to the peak of glucose level at 48 h of admission concerning the type of feeding.

Type of feeding	Peak glucose level on 48 h of admission					
	Induced hyperglycemia	Normoglycemia	Hyperglycemia			Total
			Mild	Moderate	Severe	
Nothing per oral (NPO)	0 (0%)	0 (0%)	0 (0%)	1 (4.5%)	0 (0%)	1 (0.3%)
Oral	4 (50%)	17 (53.1%)	25 (75.8%)	13 (59.1%)	128 (65.6%)	187 (64.5%)
Parenteral	1 (12.5%)	5 (15.6%)	3 (9.1%)	1 (4.5%)	33 (16.9%)	43 (14.8%)
Parenteral and Ryle	1 (12.5%)	8 (25%)	2 (6.1%)	6 (27.3%)	29 (14.9%)	46 (15.9%)
Ryle	2 (25%)	2 (6.3%)	3 (9.1%)	1 (4.5%)	5 (2.6%)	13 (4.5%)
Pearson Chi-square	Value = 33.361 P-value = 0.007					

were 250 patients (86.2%); 33 of them were mild hyperglycemia, 22 were moderate hyperglycemia and 195 were severe hyperglycemia. This is consistent with the results of Casillas et al., 2019 study in which 50%-85% of patients admitted to ICU had severe hyperglycemia [9].

Concerning the relation between hyperglycemia detected after 48 hours of admission and diabetes; 250 patients were hyperglycemic (86.2% of the study population), 65.2% of them were diabetic. Only 87 patients were hyperglycemic and non-diabetic (i.e., stress hyperglycemia). In Godinjak et al. study [8], the incidence of hyperglycemia was 54%, of them, 35% were diabetic and 19% were stress hyperglycemia. This difference may be due to the small sample size in Godinjak et al. study (100 patients), in comparison to 290 patients in our study. The incidence of stress hyperglycemia was 64% among 50 ICU patients in Temel et al. [6] study, whereas in Cely et al. [10], the incidence of hyperglycemia was 23% in 100 medical ICU patients. However, their study determined hyperglycemia depending on blood glucose levels during the first 5 days of admission, but our study used peak blood glucose levels during the first 48 hours of admission.

Table 5. The relation between the patients' mortality and the glucose level on admission and the peak of glucose level at 48 h of admission.

Fate	Glucose level on admission					
	Hypoglycemia	Normoglycemia	Hyperglycemia			Total
			Mild	Moderate	Severe	
Positive mortality	4 (50%)	34 (41%)	18 (32.7%)	8 (66.7%)	50 (37.9%)	114 (39.3%)
Ward transferral	4 (50%)	49 (59%)	37 (67.3%)	4 (33.3%)	82 (62.1%)	176 (60.7%)
Pearson Chi-square	Value = 5.355 P-value = 0.253					
	Peak glucose level on 48 h of admission					
	Induced hyperglycemia	Normoglycemia	Hyperglycemia			Total
			Mild	Moderate	Severe	
Positive mortality	4 (50%)	12 (37.5%)	14 (42.4%)	12 (54.5%)	72 (36.9%)	114 (39.3%)
Ward transferral	4 (50%)	20 (62.5%)	19 (57.6%)	10 (45.5%)	123 (63.1%)	176 (60.7%)
Pearson Chi-square	Value = 3.167 P-value = 0.530					

Concerning association with steroid usage, our study did not detect a statistically significant association between glucose levels and steroid use. But, in Donihi et al.'s study [11], hyperglycemia was a common complication of steroid therapy. This might be because, in Donihi et al. [11], patients received high doses of steroids (40 mg/day of prednisone or equivalent) for at least 2 days. Also, in our study, the effect of steroids on glucose level might appear later after our study period (initial 48 h of admission). Regarding association with circulatory supports, there was no statistically significant correlation between glucose levels and usage of circulatory supports as norepinephrine. This might be because norepinephrine plays a little role in increasing plasma glucose levels [12].

Concerning mortality as a primary outcome, 39.2% of patients who developed hyperglycemia, and 37.5% of patients with normoglycemia died. Our study did not detect a statistically significant association between hyperglycemia and mortality. Marik and Bellomo [13] revealed that acute illness-induced hyperglycemia was an adaptive response that increased the host's chances of survival. Many trials in critically ill patients [14–16] failed to show significant improvement in mortality with intensive glycemic control. Moreover, mortality risk increased with tight glycemic control [17,18]. In a meta-analysis including 13,567 critically ill patients, Griesdale et al. [19] found a favorable effect of intensive insulin therapy (IIT) on mortality only among surgical ICU patients, but there was a sixfold rise in the incidence of hypoglycemia with IIT in all ICU patients.

Also, inconsistency with our study, Green et al. [20] found that stress hyperglycemia was not predictive of mortality in adults with sepsis after correction of blood lactate levels. Moreover, Tiruvoipati et al. [21] revealed that patients admitted with septic shock and developed stress hyperglycemia had significantly lower mortality than patients with normal blood glucose levels, indicating that hyperglycemia is an adaptive response for survival. Cichosz and Schaarup [22] found that hyperglycemia is predominant in ICU and non-diabetic patients, and it is strongly associated with mortality. Also, hyperglycemia in patients with acute myocardial infarction (AMI) was associated with increased mortality [23–27]. But, our study did not detect a statistically significant difference in mortality between different groups of glucose levels and in patients with AMI. This might be attributed to population types or sample size.

In our study, the incidence of hypoglycemia on admission was 2.75% but no patient was hypoglycemic during the initial 48 hours of admission, suggesting that hypoglycemia can be an avoidable event in ICU by close monitoring of blood glucose level especially with patients on an insulin infusion. Moreover, patients who were hypoglycemic on admission became hyperglycemic; which might be secondary to a 25% glucose infusion to correct their hypoglycemia on admission.

Concerning secondary outcomes, hyperglycemic patients had a statistically significant longer period on mechanical ventilation and ICU stay than others. This is in agreement with Temel et al. [6] and Callahan and Supinski [28] who revealed that hyperglycemia was a risk factor for ICU-acquired weakness that prolonged the duration of mechanical ventilation. Also, Becker et al. [29] found that suboptimal hyperglycemic control (>180 mg/dl) during ICU stay was significantly associated with increased ICU and hospital stay.

5. Conclusion

The incidence of hyperglycemia was high on ICU admission and after 48 hours, and it was more common in diabetics. Glucose intolerance in critically ill patients was not related to associated diseases or the cause of admission. Vasopressors and steroids were not risking factors for glucose intolerance during the initial 48 hours of admission. Hyperglycemia was associated with increased duration of mechanical ventilation and total days in the intensive care unit. There was no significant difference between normoglycemic and hyperglycemic patients regarding the incidence of mortality.

5.1. Limitations and recommendations of our study

The relatively small number of patients could limit the strength of results and conclusions obtained from this study. Also, the study involved only two centers. So,

the effects of other population types were not evaluated. We recommend doing more studies in different centers and different populations so that we can extrapolate the results.

Disclosure statement

No potential conflict of interest was reported by the authors.

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