Admission Hyperglycemia: is it a Predictor of the Outcome of Postoperative Mechanically-ventilated ICU Patients?

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Abstract: ***Objectives:*** To estimate the at admission levels of random blood glucose (RBG), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) and their correlation to survival of patients admitted to surgical ICU. *Patients & Methods:* All adults patients admitted to surgical ICU for postoperative care and mechanical ventilation were enrolled in the study. All patients were clinically evaluated as regards illness severity using the Acute Physiology and Chronic Health Evaluation (APACHE II) and the simplified Therapeutic Intervention Scoring System (TISS-28) and blood samples were obtained for estimation of RBG and serum IL-6 and TNF-α levels. Patients were categorized according to at admission RBG level into normoglycemic or hyperglycemic (RBG >140mg/dl). *Results:* The study included 123 patients admitted to ICU and receiving mechanical ventilation; 27 patients were diabetics, 29 patients were hyperglycemic non-diabetics and 67 patients were normoglycemic. Twenty-eight patients died (22.8%), 10 normoglycemic (14.9%), 10 diabetics (37%) and 8 hyperglycemic non-diabetic (27.6%) patients. Estimated at ICU admission serum levels of IL-6 and TNF-α were significantly higher in hyperglycemic compared to normoglycemic patients and in diabetic compared to non-diabetic hyperglycemic patients. Estimated at ICU admission RBG and serum levels of IL-6 and TNF-α were significantly higher in non-survivors compared to survivors and in non-survivors hyperglycemic patients compared to non-survivors normoglycemic patients with non-significantly higher levels in diabetics compared non-diabetics. There was a positive significant correlation between levels of RBG and serum IL-6 and TNF-α. Levels of RBG and serum IL-6 showed a negative significant correlation with survival. Regression analysis defined at admission RBG level and serum level of IL-6 as bad predictors for survival. Conclusion: Elevated RBG levels at time of ICU admission is a frequent event accounting for about 30% and is associated with elevation of serum pro-inflammatory cytokines and may be a predisposing factor for development of additional morbidities and mortalities in non-diabetic postoperative critically ill mechanically ventilated patients.

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1. Introduction

The acute and chronic phases of critical illness are associated with distinct endocrine alterations. Acute endocrine adaptations to the severe stress of critical illness, comprising an activated anterior pituitary function are one of compensatory mechanisms. However, these adaptations disappear or wane during the prolonged phase of critical illness wherein reduced pulsatile secretion of different anterior pituitary hormones and the so-called "wasting syndrome" occurs **(Ellger *et al.*, 2005)**.

Due to the diabetes pandemic, the number of diabetic patients admitted to the intensive care unit (ICU) increases. Diabetic patients admitted to the ICU are more vulnerable for developing complications as compared to non-diabetic patients. Hyperglycemia is a common problem encountered in hospitalized patients, especially in critically ill patients and those with diabetes mellitus. Uncontrolled hyperglycemia may be associated with complications such as fluid and electrolyte disturbances and increased infection risk **(Ainla *et al.*, 2005; Butler *et al.*, 2005).**

Chronic hyperglycemia is patho-physiologically different from acute hyperglycemia. Acute hyperglycemia is a prognostic factor for mortality in critically ill patients either in the presence or in the absence of diabetes mellitus **(Gabbanelli *et al.*, 2005)**. Stress hyperglycemia in these patients develops from increased gluconeogenesis and insulin resistance due to increased catecholamine levels **(Mizock, 2001)**. **Miranda & Castanon (2004)** reported that admission hyperglycemia is statistically related to distinct changes of humoral and cellular immune functions. Furthermore, elevated glucose concentrations at admission are associated with increased ICU mortality rate **(Ishihara *et al.*, 2006)**.

Cytokines initiate, control and influence a number of biological processes like inflammation, sepsis and wound healing. With regard to their functions, all cytokines behave pleiotropic and redundant. In the case of auto/paracrinal regulation they are characterized by minimal effective concentrations, fast stimulation ability as well as short activity and presence time. However, it must be considered that plenty of diseases

may influence the systemic levels of proinflammatory cytokines **(Fieguth *et al.*, 2003)**.

Glucose is proinflammatory and even a 75-g glucose load given orally to normal subjects results in profound oxidative stress and inflammatory changes at the cellular and molecular level. This occurs even without an increase in plasma glucose concentrations into the pathological range and in spite of endogenous insulin secretion **(Mohanty, 2000)**. Therefore, if high plasma glucose concentrations are maintained, they can be expected to be profoundly proinflammatory, especially if endogenous insulin secretion is inhibited **(Dhindsa, 2004)**.

The most obvious findings related to hyperglycemia included reduced neutrophil activity, e.g., chemotaxis, formation of reactive oxygen species, phagocytosis of bacteria, despite accelerated diapedesis of leukocytes into peripheral tissue, as well as specific alterations of cytokine patterns with increased concentrations of the early pro-inflammatory cytokines. Furthermore, a reduction of endothelial nitric oxide formation takes place, thus decreasing microvascular reactivity to dilating agents such as bradykinin, and complement function, e.g., opsonization, chemotaxis is also impaired **(Turina *et al.*, 2005)**.

This prospective comparative study aimed to investigate the association between ICU admission random blood glucose (RBG) concentrations and early proinflammatory cytokines; namely interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) and its correlation to survival of patients admitted to surgical ICU.

2. Patients & Methods

The current study was conducted at Aljedaani group of hospitals under supervision of Ibn Sina National College (K.S.A.) & King Saud Medical City (K.S.A.) and Dar Elshefa hospital, Benha, Egypt from December 2009 till may 2012. After approval of the study protocol and obtaining patients' near relative written fully informed consent, all adults admitted to hospital ICU, which is dedicated primarily but not exclusively to surgical patients and receiving mechanical ventilation were enrolled in the study.

Baseline demographic and clinical data were obtained. All patients were clinically evaluated as regards illness severity using the Acute Physiology and Chronic Health Evaluation (APACHE II) **(Knaus *et al.*, 1985)** and the simplified Therapeutic Intervention Scoring System (TISS-28) **(Miranda *et al.*, 1996)**; higher scores indicate more severe illness and a higher number of therapeutic interventions, respectively. For the TISS-28 score, each therapeutic intervention was assigned 1 to 4 points, and the points are summed daily to obtain the overall score. For APACH-II score, zero points were usually assigned for the neurologic evaluation, since the majority of patients were sedated.

Patients were categorized according to at admission RBG level into normoglycemic or hyperglycemic. Hyperglycemia was considered according to contemporary medical practice which stated that hyperglycemia under stress conditions if RBG was >140 mg/dl and should only be treated with insulin if blood glucose levels are >200 mg/dl **(Mizock, 1995).**

Blood samples were withdrawn on admission and divided into two tubes, one in fluoride containing tube to prevent glycolysis for estimation of random blood glucose levels **(Tietz, 1995)**. The other part of blood sample was allowed to clot naturally and then centrifuged and supernatant was separated and stored at -20^{o}C till assayed for serum levels of interleukin-6 and tumor necrosis factor-α.

Quantitative assay of TNF-α in serum:

Tumor necrosis factor-α (TNF-α) was measured in serum using a commercially available ELISA kit (RayBio®), it is an in vitro enzyme- linked immunosorbant assay for the quantitative measurement of human TNF- alpha in serum, plasma. This assay employs an antibody specific for TNF- α coated on 96-well plate. This technique was done according to the manufacturer's instruction. Standards and samples were pipette into the wells and TNF- α present in samples were bound to the wells by the immobilized antibody. The wells were washed and biotinylated anti-human TNF- α antibody was added. After washing away unbound biotinylated antibody, horse raddish peroxidase –conjugated streptavidin was pipette to the wells. The wells were again washed, a tetramethylbenzidine (TMB) substrate solution was added to the wells and color developed in proportion to the amount of TNF- α bound. The stop solution (sulfuric acid) was added and color changed from blue to yellow, and the intensity of color was measured at 450 nm **(Beutler *et al.*, 1985)**.

Quantitative assay of IL-6 in serum:

Interleukin-6 (IL-6) was measured in serum using a commercially available ELISA kit (Quantikine, USA), for the quantitative determination of human interleukin 6 (IL-6) concentrations in cell culture supernates, serum, and plasma. This assay employs the quantitative sandwich enzyme immunoassay technique. This technique was done according to the manufacturer's instruction. A monoclonal antibody specific for IL-6 has been pre-coated onto a microplate. Standards and samples were pipette into the wells and any IL-6 present was bound by the immobilized antibody. After washing away any unbound substances, an enzyme-linked polyclonal antibody specific for IL-6 was added to the wells. Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution was added to the wells and color developed in

proportion to the amount of IL-6 bound in the initial step. The color development was stopped by sulfuric acid and the intensity of the color was measured at 450 nm **(Engvall & Perlmann, 1972)**.

Statistical analysis

Obtained data were presented as mean±SD, ranges, numbers, percentages and ratios, and median values. Results were analyzed using Wilcoxon (Z-test) test for unrelated data and Chi-square test. Possible relationships were investigated using Pearson linear regression. Predictors for survival were evaluated using the Regression analysis (Stepwise Method). Statistical analysis was conducted using the SPSS (Version 15, 2006) for Windows statistical package. *P* value <0.05 was considered statistically significant.

3.Results

The study included 123 patients admitted to ICU and receiving mechanical ventilation. There were 94 males (76.4%) and 29 females (23.6%); with mean age of 65.2±10.8; range: 49-82 years. The mean BMI was 33.1±3.8; range: 24.4-44.4 kg/m^2. Mean APACHE II score at first 24 hrs was 9.7±1.9; range: 6-13; median score=10. There were 72 patients (58.5%) had APACHE score≥10 and 51 patients (41.5%) with APACHE score <10. Mean TISS-28 score at first 24 hours was 42.5±3.3; range: 36-48; median score=41. There were 77 patients (62.6%) with TISS-28 score ≥41 and 46 patients (37.4%) with TISS-28 score <41 (Table 1).

Estimated at ICU admission RBG level defined 56 hyperglycemic patients (45.5%) with mean RBG level of 269.3±34.5; range: 215-360 mg/dl and 67 normoglycemic patients (54.5%) with a mean RBG level of 125±16.9; range: 85-160 mg/dl. Out of the hyperglycemic patients, 27 patients were diabetic; 11 patients were type-1 diabetics and 16 patients were type-2 diabetics. Mean RBG of diabetic patients was significantly (Z=4.116, p<0.001) higher compared to non-diabetic hyperglycemic patients, (Fig. 1).

Through the study period 28 patients died for a mortality rate of 22.8%, 10 normoglycemic (14.9%), 10 diabetics (37%) and 8 hyperglycemic non-diabetic (27.6%) patients. Ten patients developed ARDS, 7 patients developed SIRS, 5 had MOD, 3 pulmonary embolism and 3 acute renal failure. There was a non-significant difference between survivors and non-survivors as regards age, sex, BMI, APACHE II and TISS-28, (Table 2).

Estimated at ICU admission serum levels of IL-6 was significantly higher in hyperglycemic patients, irrespective being diabetic or not compared to normoglycemic patients and was significantly (Z=2.730, p=0.006) higher in diabetic compared to non-diabetic hyperglycemic patients, (Fig. 2). Estimated at ICU admission serum levels of TNF-α was significantly higher in hyperglycemic patients, irrespective being diabetic or not compared to normoglycemic patients and was significantly (Z=3.173, p=0.002) higher in diabetic compared to non-diabetic hyperglycemic patients, (Fig. 3). Estimated at ICU admission RBG and serum levels of IL-6 and TNF-α were significantly (p<0.05) higher in non-survivors compared to survivors and in non-survivors hyperglycemic patients, irrespective being diabetic or not compared to non-survivors normoglycemic patients with non-significantly (p>0.05) higher levels in diabetics compared non-diabetics, (Table 3).

There was a positive significant correlation between RBG levels and serum levels of IL-6 and TNF-α. However, levels of RBG and serum IL-6 showed a negative significant correlation with survival, while the correlation was negative non-significant correlation with serum levels of TNF-α, (Table 4).

Table (1): Baseline at ICU admission patients' enrollment data

Data		Findings
Age (years)		65.2±10.8 (49-82)
Sex; M:F		94:29
BMI (kg/m^2)		33.1±3.8 (24.4-44.4)
APACHE II score at 1st 24-hrs	Range	6-13
	Median	10
	Number (%) with score ≥ median score	72 (58.5%)
TISS-28 score at 1st 24-hrs	Range	36-48
	Median	41
	Number (%) with score ≥ median score	77 (62.6%)

Data are presented as mean±SD & numbers; ranges & percentage are in parenthesis BMI: body mass index

Table (2): Baseline characteristic of patients categorized according to outcome

Characteristic	Survivors (n=95)	Non-survivors (n=28)
Age (years)	64.6±10.3 (49-82)	69.9±10.5 (49-81)
Sex; M:F	75:20	19:9
BMI (kg/m2)	33.7±4 (24.4-44.4)	33.4±2.2 (28-37.3)
Diabetics: non-diabetics	17:78	10:18
Normo:hyperglycemic	57:21	10:8
Median APACHE II score	10 (6-13)	10 (6-12)
Median TISS-28 score	42 (36-48)	40.5 (38-47)

Data are presented as mean±SD, ratios & numbers; ranges are in parenthesis BMI: body mass index

Table (3): Baseline at ICU admission RBG and serum IL-6 and TNF-α levels estimated in studied patients categorized according to glycemic state and survival

Parameter		Normoglycemic (n=67)	Hyperglycemic		
			Diabetic (n=27)	Non-diabetic (n=29)	Total (n=56)
RBG (mg/dl)	Survivors	121.3±13.9 (85-140)	260.2±29.5* (215-300)	250.6±28.9 (220-315)	255.8±29.2* (215-315)
	Non-survivors	131.5±7.5‡ (115-140)	291±24.7*‡ (245-325)	288.3±33.8‡ (235-325)	289.8±28.2*‡ (235-325)
	Total	122.8±13.6 (85-140)	293.7±25.4*† (245-345)	246.6±25.1* (215-290)	269.3±34.5* (215-360)
IL-6 (ng/ml)	Survivors	1.92±0.41 (1.15-2.65)	2.98±0.48* (1.9-3.7)	2.69±0.8* (1.9-4.1)	2.82±0.7* (1.9-4.1)
	Non-survivors	2.68±0.6‡ (1.8.65)	3.45±0.57*‡ (2.15-4.1)	2.96±0.47*‡ (2.05-3.65)	3.23±0.57*‡ (2.05-4.1)
	Total	2.04±0.52 (1.15-3.65)	3.28±0.62*† (2.05-4.1)	2.73±0.52* (1.9-3.7)	3±0.63* (1.9-4.1)
TNF-α (ng/ml)	Survivors	1.5±0.35 (0.85-1.95)	1.9±0.56* (1.05-3)	1.78±0.57* (1.05-2.8)	1.83±0.56* (1.05-3)
	Non-survivors	1.87±0.47‡ (1.2-2.6)	2.5±0.5*‡ (1.9-3)	2.03±0.59*‡ (1.25-3)	2.29±0.57*‡ (1.25-3)
	Total	1.56±0.39 (0.85-2.6)	2.34±0.49 *† (1.6-3)	1.81±0.59* (1.05-3)	2.06±0.6* (1.05-3)

Data are presented as mean±SD & numbers; ranges & percentage are in parenthesis
*: Significance versus normoglycemic patients †: Significance versus hyperglycemic non-diabetic patients
‡= Significant versus survivors RBG: random blood glucose
IL-6: interleukin-6 TNF-α: tumor necrosis factor-α

Table (4): Correlation coefficient "r" between at admission levels of RBG and serum IL-6 and TNF-α levels and with survival

	RBG (mg/dl)		Survival	
	"r"	p	"r"	*p*
RBG (mg/dl)	-	-	-0.312	0.005
IL-6 (pg/ml)	0.716	<0.001	-0.294	0.008
TNF-α (pg/ml)	0.559	<0.001	-0.082	>0.05

r= Pearson's correlation coefficient RBG: random blood glucose
IL-6: interleukin-6 TNF-α: tumor necrosis factor-α

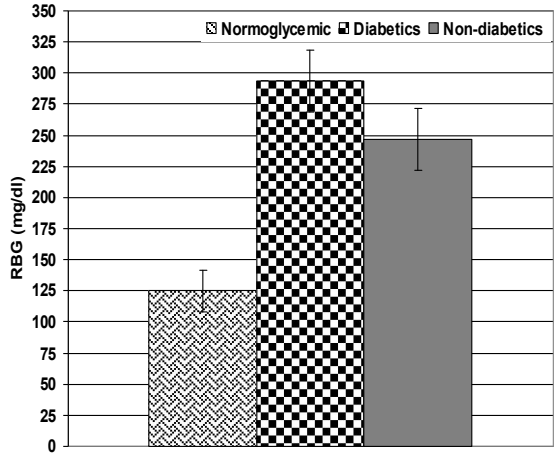

Fig. (1): Mean (±SD) RBG levels estimated in studied patients categorized according to glycemic status

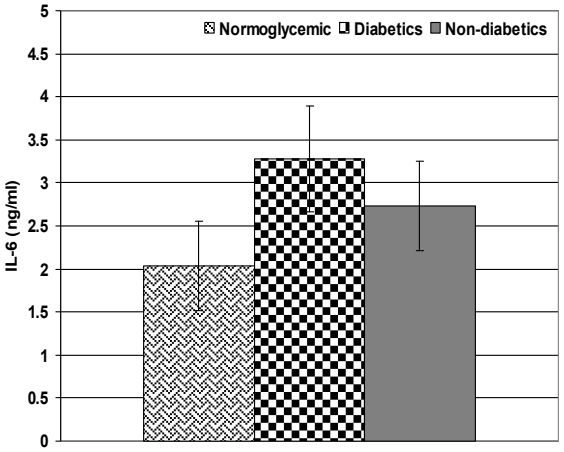

Fig. (2): Mean (±SD) serum IL-6 levels estimated in studied patients categorized according to glycemic status

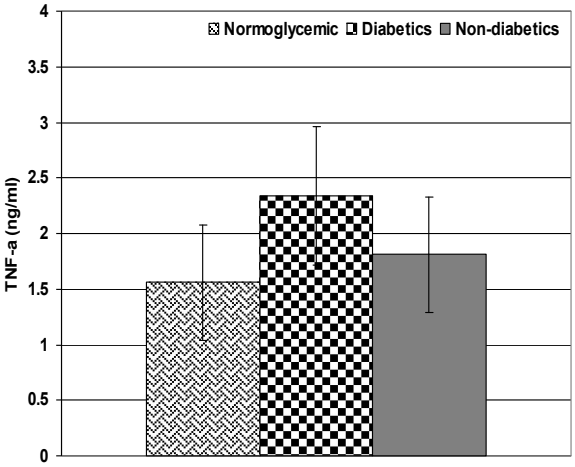

Fig. (3): Mean (±SD) serum TNF-a levels estimated in studied patients categorized according to glycemic status

Using regression analysis to determine the factors that most significantly affect survival rate when determined at admission, revealed that at admission RBG level (β=-0.322, p=0.003), followed by at admission serum level of IL-6, (β=-0.228, p=0.033) and lastly patients' age, (β=-0.202, p=0.041), whereas other factors as sex, previous history of diabetes, APACH II and TISS-28 scores and serum TNF-α were non-significantly affecting the survival rate.

4. Discussion

The current study detected a frequency of hyperglycemia of 30.2% in patients who were non-diabetic depending on preoperative investigations and documentations of nearest relatives who assured that these patients were non-diabetic and never received medications for diabetes. Review of literature showed discrepant frequency of hyperglycemia among non-diabetic patients; **Wasmuth *et al.* (2004)** and **Fish *et al.* (2007)** reported that 39.7% and 41%, respectively, of patients admitted to ICU were presented with hyperglycemia. **Palacio *et al.* (2008)** documented that hyperglycemia is present in one-fourth of children admitted to the hospital, most of them without a history of diabetes prior to admission. **Farrokhi *et al.* (2011)** documented that hyperglycemia is present in 40% of critically ill patients and in up to 80% of patients after cardiac surgery, while **Tayek & Tayek (2012)**, found that approximately 17% of patients admitted to hospital have new onset hyperglycemia and 24% have diabetes mellitus.

Such discrepant frequencies could be attributed to the pre-determined level of blood glucose as a cutoff point for development of hyperglycemia; in line with predetermined cutoff point for RBG in the current study >140 mg/dl, **Farrokhi *et al.* (2011)**, **Lee *et al.* (2011)** and **Soysal *et al.* (2012)** defined in hospital hyperglycemia as any glucose value >140 mg/dl, while **Tayek & Tayek (2012)** identified new onset hyperglycemia at fasting blood glucose >125 mg/dl or RBG >199 mg/dl.

At admission, serum IL-6 and TNF-α levels were significantly higher in hyperglycemic patients compared to normoglycemic patients and in diabetics compared to hyperglycemic non-diabetic patients. These results agreed with the experimental work of **Ling *et al.* (2005)** who found that hyperglycemic animals had significantly higher levels of cytokines compared with controls, indicating that prior hyperglycemia can enhance the systemic inflammatory response to a moderate endotoxin dose. Also, **Turina *et al.* (2005)** reported that acute hyperglycemia affects all major components of innate immunity and impairs the ability of the host to combat infection, as well as specific alterations of cytokine patterns with increased concentrations of TNF-α and IL-6.

Through the study period 28 patients died for a mortality rate of 22.8%, 10 normoglycemic (14.9%), 10 diabetics (37%) and 8 hyperglycemic non-diabetic (27.6%) patients. Ten patients developed ARDS, 7 patients developed SIRS, 5 had MOD, 3 pulmonary embolism and 3 acute renal failure. Moreover, at admission RBG levels were significantly higher in non-survivors compared to survivors and in hyperglycemic non-survivors compared to normoglycemic non-survivors. These results agreed with **Stollberger *et al.* (2005)** who reported that case fatality was 18% among non-diabetic patients who developed hyperglycemia at admission to ICU. Moreover, **Cheung *et al.* (2005)** and **Sung *et al.* (2005)** reported that increased blood glucose levels were associated with an increased risk of cardiac complications, infection, systemic sepsis, acute renal failure and death and that the mortality of patients admitted to ICU was 4.3 and 2.2 times, respectively, higher in patients developed hyperglycemia compared to normoglycemic patients.

Also, **Leonidou *et al.* (2008)** reported that a total of 42.2% of patients with severe sepsis had baseline hyperglycemia with 17.7% having sepsis-induced stress hyperglycemia and a higher percentage of septic patients with stress hyperglycemia died compared with patients with normal glucose levels (42.5% versus 13.7%) and diabetics (42.5% versus 24.6%).

There was a negative significant correlation between survival and levels of RBG and serum IL-6. Regression analysis defined at admission RBG level as the most significant predictor of high mortality rate followed by at admission serum level of IL-6 and lastly patients' age. In hand with these findings; **Liu-deRyke *et al.* (2009)** reported an overall hospital mortality of 13.2% and that non-survivors had significantly higher glucose levels at admission compared to survivors and also found admission and day-1 peak glucose were better predictors for mortality compared to hospital days 2-5 glucose levels. **Aşılıoğlu *et al.* (2011)** detected a moderately significant positive correlation between admission blood glucose and severity of head trauma, mean admission glucose level of non-survivors was significantly higher than in survivors and in patients in bad outcome group was significantly higher compared to that of the patients in good outcome group at hospital discharge and 6 months after discharge. **Nakamura *et al.* (2012)**, reported a significant positive correlation between blood IL-6 level and blood glucose level on ICU admission in the overall study population and the correlation was stronger in the non-diabetics subgroup.

The magnitude of the problem of ICU admission hyperglycemia and its impact on outcome still presenting matter of controversy; however it represents a real risk for critically ill-mechanically ventilated postoperative patients depending on the following data; first, glucose and lipid administration were shown to result in oxidative and inflammatory stress and total parentral nutrition which is a common policy for provision of nutrients to critically ill patients was accused as a cause for induction of hyperglycemia in non-diabetics **(Lee *et al.*,2011)**. Moreover, **Yang *et al.* (2012)**, demonstrated that the rapid onset of hyperlipidemia, hepatosteatosis and adipose tissue hypertrophy by ingestion of a diet high in fat and sucrose may possibly be due to the rapid response of lipogenic, insulin signalling and inflammatory genes.

Second, insulin, the hormone secreted in response to glucose and macronutrient intake, was found to suppress reactive oxygen species generation and the activation of inflammatory mechanisms **(Aljada *et al.*, 2002)**. Thus, glucose was shown to be proinflammatory while insulin is anti-inflammatory, in support of such assumption, **Monge *et al.* (2007)** reported that plasma total radical-trapping antioxidant parameter values were significantly higher in the insulin group compared with the control group at days 1 and 4 and remained stable throughout the study period in the insulin group, whereas they decreased from admission to day 1 and tended to retrieve the basal values at day 15 in the control group.

Thirdly, the restoration of normoglycemia by insulin infusion in hyperglycemic patients in a surgical ICU resulted in a 50% reduction in mortality along with several other benefits, including a reduction in the incidence of renal failure (and thus the need for dialysis), septicemia, and ICU neuropathy **(Weston *et al.*, 2007)**. However, mode of insulin therapy used, is another additional point of debit; **Benito *et al.* (2008)**, documented that intensive treatment with insulin to maintain near normoglycemia in non-diabetic patients with myocardial infarction and hyperglycemia is feasible, safe and more effective than conventional treatment and in addition, it produces attenuation of inflammatory response. On contrary, **Arabi *et al.* (2011)**, reported that intensive insulin therapy resulted in a significant decrease of soluble receptor for advanced glycation end-products and thrombomodulin at Day 7, in diabetic but not in non-diabetic patients.

The obtained results and review of literature allowed concluding that elevated blood glucose levels at time of admission to ICU is a frequent event accounting for about 30% and is associated with elevation of serum pro-inflammatory cytokines and may be a predisposing factor for development of additional morbidities and mortalities in non-diabetic postoperative critically ill mechanically ventilated patients.

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