

# The impact of the blood glucose levels of non-diabetic critically ill patients on their clinical outcome

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## Abstract

**Background:** Stress hyperglycaemia is thought to result from a hormonal response (release of catecholamines, glucocorticoids, glucagon, etc.) following stress, sepsis or trauma. Although stress hyperglycaemia is a very common finding in critically ill populations, there are many non-diabetic critically ill patients who do not develop a hyperglycaemic stress response to trauma or acute illness. We suggest that the lack of a hyperglycaemic stress response during the acute phase of a critical illness may correlate significantly with the clinical outcome of these critically ill non-diabetic patients.

**Methods:** This was a retrospective study of 700 non-diabetic critically ill patients admitted to the general intensive care unit (ICU) at Soroka Medical Center, Beer Sheva, Israel. We analyzed the clinical impact of the blood glucose levels of these patients measured during their first week of ICU hospitalization on their clinical outcome.

**Results:** Age, male gender, and the Acute Physiology and Chronic Health Evaluation (APACHE) score were found to be independent risk factors for new episodes of infection during the patients' stay in the ICU. Age and the APACHE and Sequential Organ Failure Assessment scores were found to be independent risk factors for intra-ICU mortality. In contrast, blood glucose analysis performed during the patients' stay in the ICU was not found to be an independent predictor for new infectious events or for mortality during the ICU stay.

**Conclusion:** Our study did not demonstrate an association between blood glucose levels and clinical outcomes in non-diabetic critically ill patients.

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**Key words:** glycaemia, hypoglycaemia, hyperglycaemia; critical illness; non-diabetic critically ill patients

Hyperglycaemia, even in the absence of underlying diabetes, has become increasingly recognized as a marker of a physiological "stress response" in critically ill patients. Stress hyperglycaemia is thought to result from a hormonal response (release of catecholamines, glucocorticoids, glucagon, etc.) following stress, sepsis or trauma [1]. Unopposed elevation of these "contra-insulin" hormones leads to the inability of insulin to control blood glucose levels

and to provide an intracellular glucose supply in the physiological range. The degree of hyperglycaemia, as well as the use of a strategy of insulin administration have been found to be independent predictors of outcome in both diabetic and non-diabetic critically ill populations [2, 3]. Hyperglycaemia itself has been demonstrated to be associated with increased mortality and a high rate of infectious complications [1] in critically ill ICU (intensive care unit)

patients. In previously published studies by Van den Berghe *et al.* [1, 2], intensive intravenous insulin therapy aimed at maintenance of normoglycaemia (defined as a blood glucose concentration of 80–110 mg dL<sup>-1</sup> [4.4–6.1 mmol L<sup>-1</sup>]) in critically ill patients contributed to improvement in the clinical outcome. However, the 2009 NICE-SUGAR study [3], which surveyed the outcomes of 6,104 mixed-type ICU patients, showed that a lower blood glucose target (81–108 mg dL<sup>-1</sup> [4.5–6.0 mmol L<sup>-1</sup>]) was associated with increased mortality and a higher incidence of severe hypoglycaemia [3]. The latest Survival Sepsis Campaign (SSC) guidelines (2016) [4–6] recommend maintaining the blood glucose level below 180 mg dL<sup>-1</sup> (10.0 mmol L<sup>-1</sup>) based on the NICE-SUGAR study results. The suggested trigger point for initiation of insulin therapy is a blood glucose level of > 180 mg dL<sup>-1</sup> (10.0 mmol L<sup>-1</sup>) [4, 7]. The overwhelming majority of published studies on glycaemic control in critically ill patients have dealt with diabetic patients and with markedly hyperglycaemic non-diabetic intensive care unit (ICU) patients. However, there are many non-diabetic critical care patients who do not develop a hyperglycaemic stress response on admission to the ICU and remain relatively “normoglycaemic” [8, 9]. We hypothesized that the absence of blood glucose elevation during the acute phase of a critical illness may be clinically significant and may have an important pathophysiological impact during the ICU stay of these critically ill non-diabetic patients. In the present study, we analyzed the clinical impact of the blood glucose levels measured during the first week of ICU stay on the clinical outcome of critically ill patients who did not have a documented history of diabetes.

## METHODS

The study was carried out at Soroka Medical Centre, a 1,000-bed tertiary care university hospital located in Beer Sheva, the central city of Israel's southern Negev region. We retrospectively collected the clinical and laboratory data of all the critically ill non-diabetic patients who were hospitalized in the general ICU at Soroka Medical Centre between January 2010 and December 2015. Clinical information was retrieved from our computerized Registration Information Systems (MetaVision®, iMDsoft® Israel and “OFEK” Electronic Data). The study was approved by the Human Research and Ethics Committee at Soroka Medical Centre (RN-0320-14-SOR).

## INCLUSION CRITERIA

All critically ill patients aged ≥ 18 years without a history of known diabetes who were admitted to the general ICU at Soroka Medical Centre between January 2010 and December 2015, and were hospitalized for more than 72 hours, were eligible for inclusion in the study.

## EXCLUSION CRITERIA

Patients with a history of diabetes mellitus type I or II and patients on acute or chronic steroid treatment, or with a well-documented record of a past hyperglycaemic episode were excluded from the study. In addition, patients who had been admitted to the general ICU with burns, acute pancreatitis or after pancreatic trauma or surgery or who stayed in the general ICU for less than 72 hours were excluded from the study.

## VARIABLES AND MEASURES

We recorded the patients' demographic data, the presence or absence of comorbid conditions, as well the patients' chronic drug treatment. The following laboratory findings were documented during the first week of the patients' ICU stay: blood glucose levels; mean glucose variability; arterial blood pH; and blood sodium levels. Cardiovascular and respiratory signs and the microbiological data of the study patients were also recorded, along with the following: their diagnoses on admission; their nutritional and therapeutic data during their first week of ICU stay; their Acute Physiology and Chronic Health Evaluation-II (APACHE-II) and Sequential Organ Failure Assessment (SOFA) scores; as well as their intra-ICU and intra-hospital mortality rates.

## STUDY GROUPS

The critically ill study patients without a previous history of known diabetes were divided into two groups: Group 1 incorporated patients who did not require insulin therapy during the first week of their ICU stay and Group 2 incorporated patients who required insulin therapy to achieve a blood glucose level between 140–180 mg dL<sup>-1</sup> (7.7–10.0 mmol L<sup>-1</sup>).

## DEFINITIONS

The severity of the patients' illnesses and the presence or absence of multi-organ failure were evaluated using the patients' APACHE II, Therapeutic Intervention Scoring System (TISS) and SOFA scores within 24 hours of ICU admission. The following events were defined as infectious complications during the patients' ICU stay: new primary bloodstream infections (BSIs); central line-associated BSIs (CLABSIs), wound infections and episodes of ventilator-associated pneumonia (VAP) [10, 11].

## PRIMARY ENDPOINT

In-ICU mortality was defined as the primary endpoint.

## SECONDARY ENDPOINTS

A new infectious event was defined as a secondary endpoint.

### INSULIN TREATMENT PROTOCOL

In our ICU, we use the insulin sliding scale protocol [4, 12]. The trigger point for initiating a continuous insulin infusion is a blood glucose level  $>180 \text{ mg dL}^{-1}$  ( $10.0 \text{ mmol L}^{-1}$ ) measured at least twice during a six-hour period. The insulin infusion is begun at a dose of  $1\text{--}3 \text{ IU h}^{-1}$  of short-acting regular insulin. We maintain the blood glucose level between  $140\text{--}180 \text{ mg dL}^{-1}$  ( $7.8\text{--}10.0 \text{ mmol L}^{-1}$ ). We use the same protocol for the blood glucose control of other critically ill patients (such as multiple trauma and post-operative patients). Blood glucose measurements were performed in the GICU using a blood-gas analyzer. All insulin-treated patients received the insulin by continuous infusion. Intravenous insulin was not administered to patients whose blood glucose levels did not exceed  $180 \text{ mg dL}^{-1}$  ( $10.0 \text{ mmol L}^{-1}$ ) during their ICU stay. A documented hypoglycaemic episode was defined as a blood glucose level of less than  $60 \text{ mg dL}^{-1}$  ( $3.3 \text{ mmol L}^{-1}$ ).

### STATISTICAL ANALYSIS

Categorical variables were analyzed using the Chi-square or Fisher's exact test, and continuous variables were analyzed using Student's *t*-test or the Mann-Whitney U test as appropriated. Multivariate analysis was performed using a logistic regression model and odds ratios with 95% confidence intervals were presented. We include in the multivariate model the variables with  $P < 0.05$  in a univariate analysis. All tests were two-sided, and a  $P$ -value  $< 0.05$  was deemed to indicate statistical significance. Data were analyzed using IBM SPSS 22 (NY, USA) and Epi Info 3.5.1 (CDC, GA, USA).

### RESULTS

The clinical and laboratory data of 700 critically ill patients hospitalized in our ICU during the study period were analyzed. Forty-eight patients were excluded because of incomplete medical records, leaving a total of 652 patients who were included in the study. These patients were divided into two groups: Group 1 comprised 235 patients who did not require insulin therapy for blood glucose adjustment during the first week of their ICU stay, and Group 2 comprised 417 patients who required insulin therapy for blood glucose control during the first week of their ICU stay. Early onset insulin treatment was defined as insulin administration during the first week of ICU stay in all the 417 Group 2 critically ill patients. The patients' demographic and clinical characteristics are presented in Table 1. Patients in Group 2 were significantly older ( $P < 0.001$ , Table 1) and had a higher prevalence of diagnosed sepsis on admission to the ICU ( $P < 0.001$ , Table 1) than patients in Group 1. The male gender was more prevalent in Group 1 ( $P = 0.006$ , Table 1). The proportion of trauma patients was also significantly higher

in Group 1 ( $P < 0.001$ , Table 1). There were no differences in past medical history between the two study groups.

Patients in both study groups had similar laboratory data parameters on admission to the ICU (Table 2). The total weekly caloric intake was lower in Group 1 than in Group 2 ( $P = 0.018$ , Table 2).

Vasopressor use was similar in both groups during their stay in the ICU (Table 2).

Minimal, mean and maximal blood glucose levels were measured during the first week of the patients' ICU stay. Analysis of the blood glucose data demonstrated a significant difference in the blood glucose levels between the two study groups, both on the day of admission to the ICU and during the first week of the patients' stay in the ICU ( $P$ -values  $< 0.03$ ,  $< 0.001$  and  $< 0.01$  for minimal, mean and maximal glucose levels respectively, Table 1) with Group 1 patients consistently showing lower blood glucose levels than Group 2 patients.

Of note is the fact that the initial blood glucose levels sampled on admission to the Emergency Department (ED) were also significantly lower in the Group 1 patients (Table 2).

The frequency of new major infectious events (VAP primary bacterial BSI) was significantly higher in Group 1 (the non-insulin-treated patients) compared to Group 2 (the insulin-treated patients) — in Group 1 there were 97 cases of VAP out of a total of 235 patients (41.5%) vs. 135 cases out of a total of 417 patients in Group 2 (32%) ( $P < 0.001$ ) and there were 62 BSI cases (26.4%) in Group 1 vs. 84 (20.1%) in Group 2 ( $P = 0.005$ ) (Table 3). Patients in Group 2 had higher APACHE, SOFA and TISS scores within the first 24 hours of admission to the ICU compared to the Group 1 patients ( $P < 0.001$ ,  $0.0012$  and  $< 0.001$  respectively, Table 3).

No difference was found between the two groups in regard to the frequency of hypoglycaemic episodes ( $P = 0.19$ , Table 3).

The intra-ICU and intra-hospital mortality rates were significantly higher in Group 2 compared to Group 1 ( $P = 0.001$  and  $0.033$  for intra-ICU and intra-hospital mortality respectively, see Table 3). The lengths of the patients' admissions to the ICU and to the hospital were similar in both study groups (Table 3).

Tables 4 and 5 show the results of a multivariate logistic regression analysis of critically ill patients without a previous known history of diabetes.

Age, male gender, and APACHE score and were found to be independent risk factors for new episodes of infection during the patients' stay in the ICU. Age and the APACHE and SOFA scores were found to be independent risk factors for intra-ICU mortality. On the other hand, blood glucose analysis performed during the patients' ICU stay was not

**Table 1.** The demographics, underlying conditions, admission diagnoses and laboratory data of the study patients

	Group 1 (n = 235)	Group 2 (n = 417)	P-value*
Age, years (mean ± SD)	41.9 ± 18.8	58.4 ± 20.36	< 0.001
Body mass, kg (mean ± SD)	76.7 ± 16.6	77.3 ± 15.36	0.63
Gender (male)	158/235 (67.2%)	259/417 (62.1%)	0.006
Admission diagnosis n (%):			
Peritonitis	41/235 (17.4%)	118/417 (28.4%)	< 0.001
Pneumonia	12/235 (5.1%)	51/417 (12.3%)	< 0.001
Multiple trauma	149/235 (63.4%)	173/417 (41.7%)	< 0.001
Postoperative observation	19/235 (8.1%)	32/417 (7.7%)	0.12
Other	14/235 (6%)	41/417 (9.9%)	0.024
Admission ICU <sup>a</sup> scores (units, mean ± SD):			
APACHE <sup>b</sup> score	24.32 ± 4.33	26.6 ± 5.15	< 0.001
SOFA <sup>c</sup> score	4.88 ± 2.2	5.37 ± 2.5	0.012
TISS <sup>d</sup> score	25.2 ± 7.7	25.23 ± 2.8	0.94
Laboratory data on admission to ICU:			
Blood glucose level in the ED <sup>e</sup> (mg dL <sup>-1</sup> )	146.6 ± 56.38	155.87 ± 57.03	0.04
Blood glucose level (min) (mg dL <sup>-1</sup> )	114.23 ± 24.86	121.52 ± 32.38	0.03
Blood glucose level (mean) (mg dL <sup>-1</sup> )	118.29 ± 20.14	141.23 ± 25.95	< 0.001
Blood glucose level (max) (mg dL <sup>-1</sup> )	135.08 ± 22.09	168.35 ± 37.46	< 0.01
WBC <sup>f,g</sup> (*1000 cells μL <sup>-1</sup> , mean ± SD)	13.85 ± 6.8	12.74 ± 7.1	0.07
Serum sodium <sup>g</sup> (mmol L <sup>-1</sup> )	138.85 ± 3.82	138.55 ± 4.35	0.29
PH arterial blood <sup>g</sup>	7.32 ± 0.11	7.31 ± 0.1	0.68
Haemoglobin <sup>g</sup> (g dL <sup>-1</sup> )	11.18 ± 2.15	11.34 ± 2.1	0.63
Underlying condition n (%):			
CIHD <sup>h</sup>	10/235 (4.25%)	21/417 (5.03%)	0.4
COPD <sup>i</sup>	16/235 (6.8%)	39/417 (9.3%)	0.07
HTN <sup>j</sup>	28/235 (11.9%)	52/417 (12.5%)	0.54

\*Data is considered statistically significant when  $P < 0.05$ ; <sup>a</sup>ICU — intensive care unit; <sup>b</sup>APACHE — Acute Physiology and Chronic Health Evaluation; <sup>c</sup>SOFA — Sequential Organ Failure Assessment; <sup>d</sup>TISS — Therapeutic Intervention Scoring System; <sup>e</sup>ED — emergency department; <sup>f</sup>WBC — white blood cell count; <sup>g</sup>Laboratory data parameters on admission to the I<sup>h</sup> CHID — chronic ischaemic heart disease; <sup>i</sup>COPD — chronic obstructive pulmonary disease; <sup>j</sup>HTN — hypertension

**Table 2.** Therapeutic management during the patients' intensive care unit (ICU) stay (mean ± SD, %)

	Group 1 (n = 235)	Group 2 (n = 417)	P-value*
Initiation of parenteral nutrition (day, mean ± SD)	2.1 ± 1.09	1.94 ± 0.8	0.052
Total caloric intake during first week (kcal, mean ± SD)	8028.79 ± 3623.6	8735.84 ± 3656.16	0.018
Vasopressor use (%)	71/235 (30%)	107/417 (25%)	0.128

\*Data is considered statistically significant when  $P < 0.05$

found to be an independent predictor for new infectious events or for intra-ICU mortality.

## DISCUSSION

In view of the strong correlation between hyperglycaemia and poor clinical outcome in critically ill patients [1, 2, 4, 5], continuous insulin treatment has become the cornerstone of glucose management during ICU admissions. Despite early reports of the clinical benefit of a strategy of

tight glucose control as reported by Van den Berghe *et al.* [1, 2], current guidelines [4–6] recommend maintaining the blood glucose level below 180 mg dL<sup>-1</sup> (10.0 mmol L<sup>-1</sup>). In the present study, a univariate statistical analysis showed a higher ICU mortality rate in the critically ill patients who did not have a previous history of diabetes but who, nonetheless, required insulin therapy compared with the patients who did not require any blood glucose adjustments with insulin. However, further multivariate analysis demonstrated

**Table 3.** Clinical outcome endpoints, hypoglycaemic episodes and new infectious events (mean  $\pm$  SD, %, median [IQR])

	Group 1 (n = 235)	Group 2 (n = 417)	P-value*
Hypoglycaemic episode (mg dL <sup>-1</sup> , mean $\pm$ SD)	59.13 $\pm$ 8.14	56.44 $\pm$ 7.89	0.19
New infectious event (total, %)	205/235 (87.2%)	298/417 (71.5%)	< 0.001
VAP <sup>a</sup> (%)	97/235 (41.5%)	135/417 (32%)	< 0.001
Primary bloodstream infection (BSI) (%)**	62/235 (26.4%)	84/417 (20.1%)	0.005
Central line-associated BSI (%)	8/235 (3.4%)	13/417 (3.1%)	0.08
Wound infection (%)	6/235 (2.5%)	8/417 (2%)	0.17
ICU <sup>b</sup> length of stay (day, median [IQR] <sup>c</sup> )	16 (4–61)	13 (4–72)	0.062
Hospital length of stay (day, median [IQR])	29 (8–86)	28 (4–133)	0.74
ICU Mortality (%)	22/235 (9.4%)	78/417 (18.7%)	0.001
In-hospital mortality (%)	9/213 (4%)	35/339 (10%)	0.033

\*Data is considered statistically significant when  $P < 0.05$ ; \*\*BSI incidence for Group 1 was 4.1 per 1,000 ICU days and for Group 2, 4.87 per 1,000 ICU days; <sup>a</sup>VAP — ventilator-associated pneumonia; <sup>b</sup>ICU — intensive care unit; <sup>c</sup>IQR — interquartile range

**Table 4.** Multivariate logistic regression analysis for risk factors for new episodes of infection in critically ill patients without a known history of diabetes

	OR	95% CI	P-value
APACHE <sup>a</sup> score (on admission)	1.04	1.001–1.08	0.04
Age (years)*	1.05	1.03–1.07	< 0.001
Gender (male)	2.001	1.36–2.93	< 0.001

\*Age: for each year of age; <sup>a</sup>APACHE — Acute Physiology and Chronic Health Evaluation; OR — odds ratio; CI — confidence interval

**Table 5.** Multivariate logistic regression analysis for risk factors for in-ICU mortality of critically ill patients without a known history of diabetes

	OR	95% CI	P-value
APACHE <sup>a</sup> score (on admission)	1.08	1.026–1.14	0.004
Age–years*	1.02	1.009–1.32	0.001
SOFA <sup>b</sup> score	1.05	1.0(+) <sup>#</sup> –1.16	0.04

\*Age: for each year of age; <sup>a</sup>APACHE — Acute Physiology and Chronic Health Evaluation; <sup>b</sup>SOFA — Sequential Organ Failure Assessment; <sup>#</sup>1.0(+) denotes a positive value close to 1; OR — odds ratio; CI — confidence interval

no correlation between any level of blood glucose and ICU mortality. Moreover, we showed that only age, gender and disease severity (as assessed by the patients' APACHE and SOFA scores) were found to be independent predictors of increased ICU mortality among these critically ill patients.

Surprisingly, we demonstrated that the patients in the non-insulin-treated group had a higher incidence of new infectious events, especially new VAP and primary BSI events during their ICU stay, in comparison with patients without a previous history of diabetes who required insulin therapy. This phenomenon might be related to the large number of patients with multiple trauma in both study groups (40–60%). Previous reports [9, 13] have indeed shown that multiple trauma correlates strongly with a relatively high incidence of VAP (especially in the presence of acute lung injury) and also correlates with non-catheter-related BSIs.

As noted above, a subsequent multivariate analysis did not demonstrate a relationship between the frequency of

new infectious events and the patients' blood glucose levels. In our study, age, male gender, and severity of disease (as assessed by the APACHE score) were found to be independent predictors of a high frequency of new infectious events during the patients' ICU stay. Age and severity of critical illness have been well documented as predictors of new infectious events in previously published studies [14]. However, we also found that male gender was an independent predictor for ICU mortality among these critically ill patients. This was an unexpected finding which has not been reported in previous studies.

In our study, we investigated non-diabetic critically ill patients without a known history of diabetes. The majority of previously published studies regarding glycaemic control in the non-diabetic critically ill population have yielded controversial results. Thus, some studies (Arabi *et al.* [13]) found that no benefit derived from intensive intravenous insulin therapy and that there was no difference in outcome between patients with and without diabetes. In contrast,

Krinsley *et al.* [15], using a moderately tight glycaemic control protocol, found a significant reduction in the mortality rate in non-diabetic patients compared to the mortality rate in patients with known diabetes.

Transient hyperglycaemia is common in hospitalized patients, especially among those admitted to an ICU. The neuroendocrine response to acute stress is characterized by excessive gluconeogenesis, glycogenolysis, and insulin resistance resulting in stress hyperglycaemia [16]. The stress response involves functional changes in the hypothalamic-pituitary-adrenal axis and in the sympathoadrenal system with resultant development of insulin resistance in critically ill patients, even in those without diabetes [17]. In general, the severity of stress hyperglycaemia is related to the intensity of the stress causing factors [16, 17]. Consequently, poor clinical outcomes and high mortality rates could well be related to the proinflammatory, prothrombotic and pro-oxidant adverse effects of uncontrolled stress hyperglycaemia in acutely ill patients [16, 18]. In fact, a majority of critically ill multiple trauma patients develop the systemic inflammatory response reaction which is often associated with a hypermetabolic profile [19, 20]. Another important pathological factor related to the development of a hypermetabolic state and a poor clinical outcome in multiple trauma patients is oxidative stress [19, 20]. Furthermore, there are a number of genetic factors involved in hypermetabolic activity in critically ill multiple trauma patients such as hereditary expression of mitochondrial RNA [19, 20].

However, there remains a group of critically ill patients who, for reasons that are as yet unexplained, have an atypical euglycaemic response to stress on admission to the ICU, manifesting as blood glucose levels of 71–140 mg dL<sup>-1</sup> (3.9–7.8 mmol L<sup>-1</sup>), or only a mild hyperglycaemic response, manifesting as blood glucose levels of 141–180 mg dL<sup>-1</sup> (7.8–10.0 mmol L<sup>-1</sup>). The existence of this type of atypical response to stress raises questions regarding the functional competence of the hypothalamic-pituitary-adrenal axis in these critically ill patients.

In planning the present study, we hypothesized that the mortality rate might be even higher in critically ill patients group whose blood glucose levels did not exceed 180 mg dL<sup>-1</sup> (10 mmol L<sup>-1</sup>) and who did not require blood glucose adjustments with insulin compared to the patients without a previous history of diabetes who did require insulin therapy. However, after a multivariate analysis our data did not show any association between ICU mortality and the blood glucose levels in both study groups. It follows that if the APACHE scores and the proportion of male gender had been equivalent in both study groups, the ICU mortality rate would have been the same without any relationship to the patients' blood glucose levels. Theoretically,

the mortality rate could be affected in either of two ways: first, the theoretical mortality rate could be decreased in the insulin-treated group owing to the impact of insulin itself; or second, the theoretical mortality rate could be increased in non-insulin-treated group by an atypical lack of response to stress on the part of the hypothalamic-pituitary-adrenal axis.

Our study has a number of limitations, of which the main one is its retrospective design. Moreover, there was no definite evidence that the strategy of distribution and stratification of the data into two groups of insulin treatment was precise and optimal. Because our study was retrospective, the influence of directed, active control of insulin therapy could not be assessed. Another limitation of the study was that we did not take into consideration the potential existence of other critically ill subgroups, such as patients with blood glucose levels between 120–180 mg dL<sup>-1</sup> (6.7–10.0 mmol L<sup>-1</sup>). The significance of the patients' ICU blood glucose levels in relation to their long-term outcomes is unclear because the study did not incorporate post-hospital follow-up of the study patients.

## CONCLUSION

While the present study did not demonstrate an association between blood glucose levels and clinical outcome in non-diabetic critically ill patients, we feel that further studies are needed to better understand the clinical significance of variations in the blood glucose levels of critically ill non-diabetic patients.

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