Original Article

HYPERGLYCEMIA AND MORTALITY IN CRITICALLY ILL PATIENTS

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ABSTRACT

Objectives: To analyze the relation between serum glucose concentration and hospital outcome across the critically ill patients.

Methodology: A single-centre, retrospective study was performed at surgical and medical intensive care unit. Admission glucose, mean morning glucose, mean glucose, maximal glucose and time-averaged glucose levels were calculated for each patient. The time-averaged hyperglycemia was defined as the area under the curve above the upper limit of normal, divided by the total length of stay.

Results: Of 300 patients with a median stay of 16 days, the mortality rate was 32%. Mean fasting glucose was 121 mg/dl in survivors versus 160 mg/dl in non survivors (P=0.001). Mean admission glucose was 127 mg/dl in survivors versus 142 mg/dl in non survivors (0.03). Median time-averaged hyperglycemia was 4 mg/dl in survivors versus 17.5 mg/dl in nonsurvivors (P < 0.006). The area under the receiver operator characteristic (ROC) curve was 0.59 for time-averaged glucose and 0.73 for mean fasting glucose.

Conclusions: Whereas time-averaged hyperglycema is a useful assessment for glucose control in critically ill patients, it has no priority to admission glucose and mean fasting glucose for outcome prediction.

KEY WORDS: Critically ill patients, Glucose, Outcome.

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INTRODUCTION

A high proportion of patients suffering from an acute stress may develop hyperglycemia, even in the absence of a preexisting diagnosis of diabetes. Both human and animal studies suggest that this is not a benign occurrence and that stress-induced hyperglycemia is associated with a high risk of mortality.[1] The benefit of strict glucose control in the intensive care unit (ICU) was demonstrated by the Leuven study.[2,3] Significant reduction in morbidity and mortality was achieved in patients who were treated according to a protocol that aimed to achieve normoglycaemia. Although this represents a clear goal for algorithms, there is no

clear way to assess the performance of such algorithms.[4] In ICU patients, glycosylated hemoglobin A1C, which has proven to be an important predictor of long-term glucose control, is not a reliable marker.[5] Continuous glucose monitoring allows checking metabolic status throughout the day, but its efficacy has been seen only in short periods.[6]

In studies of acutely ill patients, regular indices of glucose regulation that have been used are admission glucose, maximum glucose, mean morning glucose and mean glucose.[7,8] All of these indices have specific drawbacks. Admission glucose, maximum glucose and mean morning glucose are all based on either a single measurement or a subset of measurements, and therefore they are not indicative of overall hyperglycemia. A single mean glucose that uses all measurements can be strongly biased by unequal time distribution between measurements, as commonly occurs in practice.[9-11] Calculating time-averaged glucose compensates for an unequal time distribution of glucose measurements. However, hypoglycemic episodes may still lower such an index, thus falsely suggesting normoglycaemia when in reality hyperglycemia is present. The time-averaged hyperglycemia as defined by the area under the glucose curve above the normal range divided by the length of stay, which is not falsely lowered by low glucose values, would be a better index of glucose regulation.[12]

We evaluated the association of time-averaged hyperglycemia and conventional glucose indices of regulation with outcome in a group of our ICU patients with a prolonged ICU stay.

METHODOLOGY

In a retrospective analysis we included all patients older than 15 years of age admitted to the medical and surgical ICU of our tertiary teaching Valiasr hospital in Arak Iran from 2005 to 2006. Because glucose control appears to be particularly important in patients with prolonged stay in the ICU, we studied only those patients who stayed for four days or longer in the ICU. Exclusion criteria were: previous history of diabetes mellitus and Glasgow Coma Scale (GCS) score <5 on admission. Age, sex, admission type and the GCS score were obtained from case records of all admitted patients to our hospital.

Whole blood samples were taken from arterial or central lines and sent to the central laboratory for glucose measurement. Admission glucose was defined as the first measurement after ICU admission. Mean morning glucose was calculated as the arithmetic mean of all measurements done between 06:00 hours and 08:00 hours. Mean glucose was calculated as the arithmetic mean of all measurements. Maximum glucose was the highest glucose determined for the entire ICU stay. To determine the time-averaged hyperglycemia of a patient, all glucose measurements performed during the ICU stays were analyzed. The first step was to interpolate all glucose values. Then, the area between this glucose curve and the upper normal range was calculated. The time-averaged hyperglycemia was defined as this area under the curve divided by the total length of stay, thus making time-averaged hyperglycemia independent of length of stay.

We chose 125mg/dl as our upper range of normal in all tests .As for other measures of glucose regulation, time-averaged hyperglycemia is expressed in milligram per deciliter (mg/dl). Thus, a patient in whom all glucose values are 150mg/dl will have a time-averaged hyperglycemia of 25mg/dl. A patient who is normoglycemic, with all measured glucose levels at 125mg/dl or less, will have a time-averaged hyperglycemia of 0.0mg/dl. Data were expressed as means and median. Differences between groups were assessed using the Mann–Whitney U test, and Chi2 analysis was used to test differences between proportions. In order to compare the validity of each test for the predicting of death in studied patients we used receiver operator characteristic (ROC) curve analysis by Medcalc software and with Chi2 test. In univariate analysis, we assessed the performance of the time-averaged hyperglycemia and other glucose-derived measures in relation to outcome. Patients were sub grouped into survivors (i.e. patients that discharged)

Table-I: Characteristics for surviving and non-surviving patients and results of univariate analysis of glucose indices

Characteristics	*Survivors*	*Non-survivors*	*P*
Number of Pt.(n [%])	204(68)	96(32)	
Male (n[%])	155(76)	65(69)	0.25
Age (years; mean ±SD)	40 ± 19	51± 20	0.001
Length of ICU stay(days)	16 (4-48)	16 (5-69)	0.51
Reason for ICU admission(n [%])			0.001
Medical	32 (56)	25 (44)	
Surgery	34 (57)	26 (43)	
Trauma	118 (74)	41 (26)	
Poisoning	20 (83)	4 (17)	
Mean fasting glucose (mg/dl)	121 (108-140)	160 (133-165)	0.001
Mean Admission glucose (mg/dl)	127 (106-159)	142 (118-173)	0.03
Mean Maximum glucose (mg/dl)	163 (138-201)	200 (165-252)	0.001
Mean glucose (mg/dl)	125 (110-156)	170 (149-189)	0.001
Time-averaged hyperglycemia [a] (mg/dl)	4 (2-34)	17.5 (10-50)	0.006

[a]Value is expressed as median (interquartile range).
ICU, intensive care unit; SD, standard deviation

and non survivors. We performed a multivariate binary logistic regression analysis with age, sex, type of admission, and all glucose-derived measures as independent parameters. Differences were considered significant for a two-tailed P value < 0.05. The Statistical Package for the Social Sciences (version 11.0.1; SPSS) were used to conduct statistical analyses.

RESULTS

Out of 351 patients admitted to the ICU, a total of 300 patients (85.5%) stayed for a period of at least four days and were included in the present study. Table-I lists the demographical data and glucose-related measures for survivors and non survivors. Trauma was the most frequent reason for ICU admission. Survivors and non survivors both stayed in the ICU for a median of 16 days. A total of 96 patients (32%) died within ICU admission. A total of 26,267 glucose measurements were performed in the 300 included patients. The mean fasting glucose concentration of all patients was 140mg/dl (108-165mg/dl) mean glucose was 147 mg/dl (125-189mg/dl), mean admission glucose was 134 mg/dl 1 (106-173mg/dl), mean maximum glucose was 181mg/dl (138-252mg/dl) and mean time-averaged hyperglycemia was 10.7 mg/dl (2-50mg/dl). The mean glucose indexes in survivors and non survivors are listed in Table-I.

Table-II: the area under each curve of tests

Type of test	*Area under the curve*	*Standard deviation*
Blood sugar on admission	0.57	0.036
Maximum blood sugar	0.68	0.035
Average of fasting blood sugar	0.73	0.033
Time-averaged hyperglycemia	0.59	0.036

Table-III: pair wise comparison of different tests

Pair Wise Comparison	*P value*
Blood sugar in admission & Maximum Blood sugar	0.007
Blood sugar in admission & Mean of fasting blood sugars	0.033
Blood sugar in admission & time-averaged hyperglycemia	0.399
Maximum Blood sugar & mean of fasting blood sugars	0.039
Maximum Blood sugar & time-averaged hyperglycemia	0.016
Mean of fasting blood sugars & time-averaged hyperglycemia	0.0001

In the univariate analysis, all glucose indexes were significantly higher in non survivors. The ROC curves of different tests are shown in Fig-1. Table-II shows the area under each curve and its standard deviation. The mean fasting glucose had the highest area under curve (0.73). Pair wise comparisons between different tests are shown in Table-III. In multivariate analysis with sex and age and reason for ICU admission, all glucose indexes remained statistically significant in the binary logistic model.

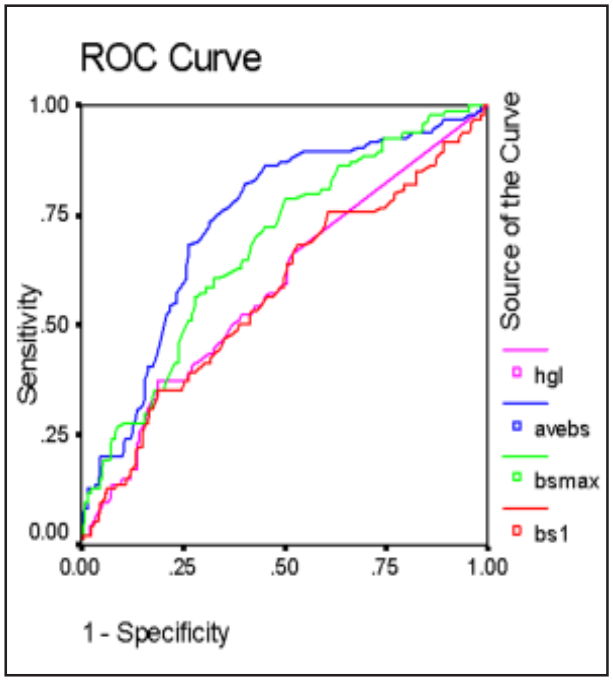

Fig-1: ROC curves of different tests. hgI, Time averaged hyperglycemia. avebs, Average of fasting blood sugar. bsmax, Maximum blood sugar.bs1, Blood sugar on admission.

DISCUSSION

This study shows that all measurements of evaluated glucose are higher in non survivors. Whereas this study supports the hypothesis that the time-averaged hyperglycemia is a useful index for quantifying glucose control, it doesn't reflects that this index is the best indicator of patient outcome.

In our study, mean fasting blood glucose had highest area under curve that means it is the better indicator for ICU mortality in this population of critically ill patients. In multivariate analysis with sex and age and reason for ICU admission, all glucose indexes remained statistically significant in the binary logistic model. An elevated admission glucose level or mean fasting glucose is associated with a worse outcome; this has been found by many investigators in various patient categories [13-18], and was also found in the present study. It seems that time-averaged hyperglycemia involves additional computation as compared with more straightforward indices and reflects the fact that it takes better account of the variation in glucose concentrations over time, and avoids the possibility that alternating high and low values will average out to yield a normal value. However, with a ROC area of 0.59, time-averaged hyperglycemia cannot serve as a useful predictor of mortality

A number of features suggest that patients with newly diagnosed hyperglycemia were more severely ill than patients with known diabetes. Although the underlying mechanisms for the development of stress hyperglycemia are

not fully understood, several potential mechanisms have been proposed. These include increased substrate availability in the form of lactate,[19-21] increased gluconeogenesis and decreased glycogenolysis due to increased secretion of counterregulatory hormones (catecholamines, cortisol, and glucagon)[22-24] and peripheral insulin resistance.[25,26] Although in such patients, the high morbidity and mortality relate to the associated illness precipitating the stress, hyperglycemia itself may contribute to morbidity by creating a toxic cellular milieu,[27-29] causing intracellular and extracellular dehydration,[30] inducing electrolyte abnormalities, and depressing immune function.[31]

Limitations of the study: It was a retrospective, strict glucose control was not a major issue at that time and relative contributions of glucose infusion or (par)enteral feeding could not be identified to the time-averaged hyperglycemia. It should be stressed that time-averaged hyperglycemia was designed to quantify hyperglycaemia and not hypoglycaemia. Prevention of hypoglycaemia is a critical requirement of any algorithm for glucose control.[3] However, unlike hyperglycaemia, hypoglycaemia is a phenomenon that tends to be relatively short-lived, and could be quantified using more straightforward measures such as the lowest glucose concentration.

Whereas time-averaged hyperglycemia is a useful assessment for glucose control in critically ill patients, it has no priority to admission glucose, maximum glucose and mean fasting glucose for outcome prediction.

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