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THE RELATION BETWEEN REGULATION OF BLOOD SUGAR IN SEPSIS AND PATIENT MORTALITY

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ABSTRACT

Aims: In this study, the relation between the regulator and counter-regulator systems of blood sugar which were impaired in heavy infection cases, the negative effects of defence and healing mechanisms of the body and the patient mortality has been studied.

Methods: 30 patients (19 males, 11 females) with severe infection (sepsis) have been scanned retrospectively. Patient data has been gathered in one common database and stratification has been made in relation to fasting blood glucose, CRP and APACHE-II rates.

Results: There is a statistically significant relationship between the high blood sugar levels of the patients and their increased CRP levels. It has been determined that blood sugar levels between 105 – 145 mg/dl provides optimal patient survival.

Conclusion: Glycaemic regulation is impaired in sepsis patients. Keeping the blood glucose levels in physiologic ranges is an important factor to be considered regarding patient survival.

Key Words: Stress, hyperglycemia, insulin resistance, sepsis

INTRODUCTION

In acute life threatening situations, a great response of stress develops in the body and one of the effects of these situations on the body is stress induced hyperglycaemia. Stress induced hyperglycaemia may occur in situations such as myocardial infarction, stroke, shock (especially septic shock) and trauma.

In the acute situations glucose metabolism changes from beginning to end, starting from cellular uptake to gene level expression. Glucose increase in the cells does not always mean mitochondrial ATP synthesis, it also activates metabolic pathways. Even though long time exposure to products of these pathways causes diseases such as diabetes, the main role of the hyperglycaemia in acute situations is worth studying (1).

The first response of the body towards the stress is the increase in levels of glucagon, growth hormone, norepinephrine, epinephrine and cortisol with the activation of the central nervous system and neuroendocrine mechanisms. These hormones especially affect the cytokine release and modify the immune response. In addition to other mechanisms, these hormones also stimulate glyconeogenesis and cause hyperglycaemia (2).

Pancreatic insulin secretion starting as a response to the increasing blood sugar levels prevents the production of hepatic glucose and enables the uptake and storage of glucose by liver, muscle and fat tissue. If pancreas is not able to create this glucose control, too much glucose is available at the cellular microenvironment and glucose goes into the cells via the carriers named GLUT. The amount of these GLUTs on the cell surface are amplified by insulin. (3)

In stressful situations, mechanisms such as hypoxia in cellular levels, adenosine production and oxidative stress became active. Hypoxia stimulates the glycogenolysis and increases the existing glucose amount (4). While this glucose is used in glycolysis, activities of phosphofructokinase-1 and lactate dehydrogenase are simultaneously stimulated by increased lactate production via decreased mitochondrial oxygen usage. With the help of this mechanism, which is described as “Warburg effect” in the tumor cells (5) in the cases of lack of oxygen in hypoxic situations, enough energy can be produced without an increase in the reactive oxygen radicals (6). Increase in the adenosine production is the result of the breakdown of ATP which released to the extracellular area under stressful conditions. Adenosine organizes the acquired and natural immunity by interacting with almost every immune cell (7). It prevents the presentiation of antigens,

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production of inflammatory cytokines and reproduction of the immune cells and contributes to cell repair and remodeling. In the last mechanism which is oxidative stress, the main reason is the production of oxygen radical and impaired cell functions as a result. Oxygen radicals are available inside mitochondria, cytoplasm, and cell membrane and when the amount is increased, it causes DNA changes and effects the glucose metabolism even though it is an indirect affect (8).

Sepsis is the systemic inflammatory response caused by the abnormal existence of bacterial antigens and it is a complex phenomenon in which all these mechanisms are included. In the beginning, there is an increase in the inhibition of the glycogen synthesis and cellular glucose uptake (9). Glucose uptake seems to have increased most in the organs such as liver, spleen, bowels and lungs which have phagocytal cells in large numbers. In short, glucose metabolism changes under the acute critical conditions such as sepsis, occurs in a way in which glucose consumption moving from creating lactates from mitochondrial oxidative phosphorylation towards other metabolic pathways. As a result, these cells consume less ATP and lose the ability to carry out important functions which translates into metabolic deficiency (10).

It is a popular view that stress hyperglycaemia is an important indicator of mortality and morbidity. However, there is also a view that hyperglycaemia which occurs during acute diseases is an adaptive response which has been protected evolutionally and which increases the survival chance of the patient. Also it has been understood that iatrogenic intervention to this complex response may be harmful. Only the patients with severe hyperglycaemia (blood sugar above 220 mg/dL) can benefit from moderate glycaemic control (11). This hypothesis may seem contradictory with the familiar diabetes pathophysiology. Hyperglycaemia related to diabetes is a chronic process which has pro-inflammatory, pro-thrombotic and pro-oxidative effects. This indicates that whether hyperglycaemia is beneficial or harmful is a question of how long and at which level hyperglycaemia prevails. Acute hyperglycaemia has been shown to limit myocardial damage after hypoxia (12), however an increase in the death rates of the cardiomyocytes which were treated with glucose for a long time (13) has also been shown. The protective effect of the acute hyperglycaemia has been thus shown, but although not yet proven, stress induced hyperglycaemia is thought to be doing harm. Severe hyperglycaemia would obviously increase serum osmolarity, cause diuresis and consequently volume deficiency. The threshold value which creates danger in stress induced hyperglycaemia is not known, however. The patients who developed a severe stress hyperglycaemia there most likely has an impaired glucose tolerance as well (11).

Due to various views in literature on stress induced hyperglycemia, this study aims to study the relationship between the regulator and counter-regulator systems of blood sugar which were impaired in heavy infection cases, the negative effects of defence and healing mechanisms of the body and the patient mortality.

MATERIAL AND METHOD

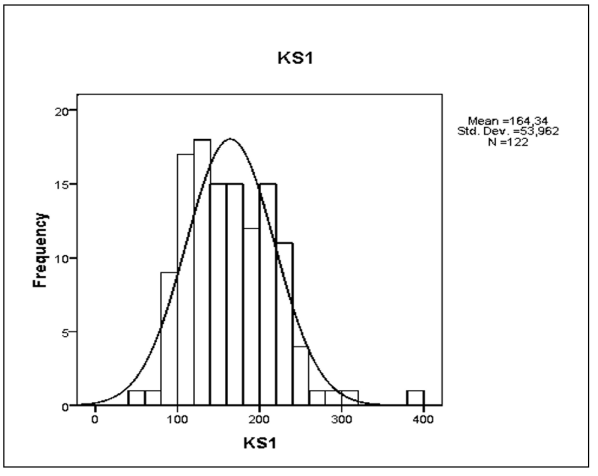
This study has been carried out by retrospectively examining the patient records belonging to patients who have been hospitalized in Trakya University Medical Faculty Hospital Intensive Care Unit. Data belonging to a total of 30 patients (19 males, 11 females) with severe infection (sepsis) have been scanned retrospectively. The criteria for the diagnosis of sepsis are the presence of known or suspected infection along with two or more SIRS (Systemic Inflammatory Response Syndrome) criteria. SIRS criteria are as follows: body temperature less than 36°C or greater than 38°C, heart rate greater than 90 beats per minute, respiratory rate greater than 20 breaths per minute, leukocytes less than 4000 cells/mL) or greater than 12,000 cells/mL or the presence of greater than 10% immature neutrophils. Fasting blood glucose levels, CRP levels and APACHE-II scores belonging to patients are recorded in one database. APACHE-II (Acute Physiology and Chronic Health Evaluation II) is one of many ICU scoring systems which determine the severity of patient's condition and is calculated in 24 hours following patient's admission in the ICU. According to the criteria such as age, temperature, mean arterial pressure, pH arterial, heart rate, respiratory rate, sodium (serum), potassium (serum), creatinine, hematocrit, white blood cell count and Glasgow Coma Scale, a score between 0 and 71 is calculated, with higher scores corresponding to a more severe disease and a higher risk of death.

Patient data explained above has been gathered in one common database and stratification has been made in relation to AKŞ (fasting blood glucose), CRP and APACHE-II rates. Confidence interval (CI) has been taken as %95 and $p<0.05$ values are accepted as meaningful. The results are given as mean±SD.

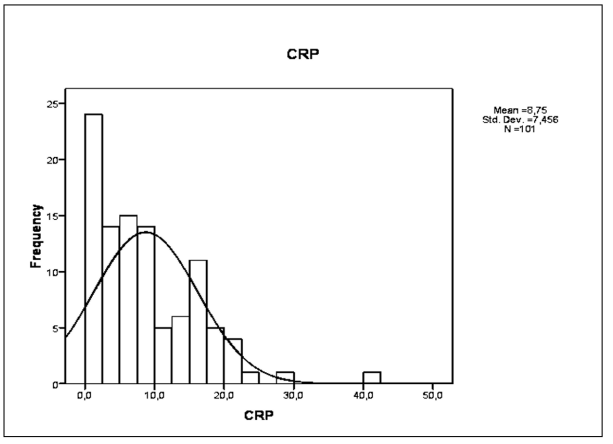
RESULTS

The age average of the patients are 64,1±18,3 years, time of hospitalization is 4,1±2,3 days and blood sugar levels are 164,3±53,9 mg/dl, CRP values are 8,7±7,5, APACHE-II score is 19,4±7,9. 18 of these patients have been discharged and 12 patients have deceased (%40 mortality).

In the correlation analysis made, there is a meaningful relationship between the high blood sugar levels of the patients and their increased CRP levels ($p<0.001$). In the ROC curve analysis: the values of blood sugar levels being under 104 mg/dl, % 94 sensitivity and %87 specificity and blood sugar levels being above 227 mg/dl % 89 sensitivity and %88 specificity shows a heightened patient mortality. It has been determined that in the regression analysis; blood sugar levels being between 105 – 145 mg/dl gives us optimal patient survivability and together with this every 10 mg/dl deviation from these levels increases the risk of mortality 2 fold.



Graphic 1: Mean daily blood glucose of patients.



Graphic 2: C-reactive protein values of patients per day.

DISCUSSION

The results obtained from this study show that blood sugar levels between 105 – 145 mg/dl leads to optimal patient survival and 10 mg/dl deviation from these levels increases the risk of mortality twice. These findings coincide with the information from previous studies that human body answers stress with hyperglycaemia. However, it should be kept in mind that hyperglycaemia can also affect mortality negatively.

Blood sugar levels below a certain level (105 mg/dl in our study) is another factor which increases mortality. Although our study cannot clearly find out the reason for that, there may be two possible causes. First explanation is that blood sugar levels below 105mg/dl indicate possible hypoglycaemia attacks. This causes neuroglycopenic and adrenergic results and creates an impairs stress responses of the body, exacerbating the prognosis of sepsis patients. Another reason why the blood sugar levels are below the required level might be explained with insufficient stress response of the patient. If the change in metabolic pathways mentioned in the introduction section and interaction of these pathways with inflammatory cells are not enough, the patient is not able to create the required stress hyperglycaemia and the prognosis would therefore be affected negatively.

The only condition required for cases to be included in this study is being in sepsis. It is unknown if the patients participating in the study to have glucose tolerance or diagnostic of diabetes mellitus before they have been admitted to the hospital. Small changes in the fasting blood glucose and HbA1c levels trigger overall mortality, especially cardiovascular mortality causes. Tayek and Tayek's results on the comparison between intensive care unit mortalities of diabetes-diagnosed patients and those who are known to be non-diabetic are as follows: At the beginning of the study the risks belonging to these groups have been thought to be equal, but interestingly the mortality rates have been found to be lower in the patients who have previously diagnosed with diabetes (14). This situation has been explained in various ways. Since the body has been in hyperglycaemia for a long time, it may have adapted to it. On the other hand, diabetic patients who suffer from bacteremia have lower mortality levels, which is a result of the fact that in prediabetics a sudden increase in blood sugar levels causes immune system dysregulation, which results in severe results of infection. Additionally the patients diagnosed with diabetes have probably been taking metabo-

lism-protecting medications such as statins, ACE inhibitors, ARBs, aspirin and calcium channel blockers. In the non-diabetic patients who probably do not take these drugs, cardiac function is more impaired, anticoagulants such as antithrombin III and protein S levels are dramatically low, incidence of coronary artery plaque formation is increased. Another element which makes the prognosis of the patients who are diagnosed with diabetes better is thought to be the fact that doctors could easily add insulin to the treatment when the patient is taken into intensive care. Thus the diabetic sepsis patient is easily protected from the negative effects of hyperglycaemia. However, what matters most is providing the intensive care patients not diagnosed with diabetes with the glycaemic control, because this group is shown to benefit from the insulin treatment more than the diabetic patients and there has been a certain decrease in mortality rates.

The results of this have shown that although hyperglycaemia occurs as a defence mechanism in sepsis patients, glycaemia levels above or below the optimal level deteriorate mortality rates. However, studies including matters such as whether the patients have previously received diabetes treatment or their glycaemic condition before they have been hospitalized for sepsis are still needed. By this means, it can be further revealed how important it is to prevent new onset hyperglycaemia in septic intensive care unit patients who have not been previously diagnosed with diabetes.

Severe infection impairs the blood sugar regulation of the sepsis patients and with the increased indicators of the infection, blood sugar regulation is further impaired. Independent from the treatment of the underlying infection, keeping the blood sugar levels in physiologic ranges, is an important factor to be considered with respect to patient survival.

Ethics Committee Approval: This study was approved by Trakya University Faculty of Medicine Scientific Researches Ethics Committee.
Informed Consent: Written informed consent was obtained from the participants of this study.
Conflict of Interest: The authors declared no conflict of interest.
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