The Association of Early Combined Lactate and Glucose Levels and Hospital Mortality in Critically ill Patients

Thesis

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By

Ahmed Ramadn Abdlaziz Abdlgawad

M. B. B. Ch.

Under Supervision of

Prof. Dr. Bahaa Elden Eweas Hassan

Professor of Anesthesia & ICU and Pain Management

Faculty of Medicine - Ain Shams University

Dr. Dina Salah Elden Mouhamed

Assistant Professor of Anesthesia & ICU and Pain Management

Faculty of Medicine - Ain Shams University

Dr. Mai Mohsen Abdlaziz Gadallah

Lecturer of Anesthesia & ICU and Pain Management

Faculty of Medicine - Ain Shams University

Faculty of Medicine
Ain Shams University
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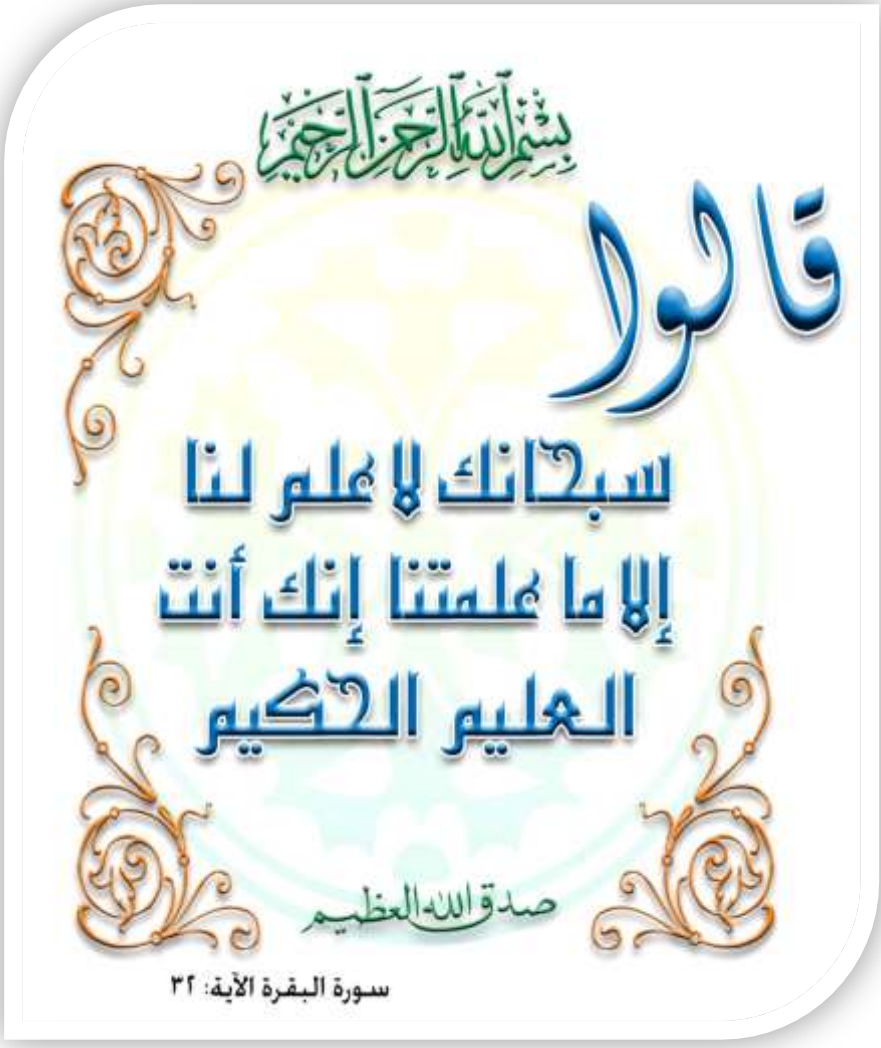
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List of Abbreviations

Abbr.	Full-term
ACTH	**:** Adrenocorticotrophic Hormone
AMI	**:** Acute Myocardial Infarction
ATP	**:** Adenosine Triphosphate
ChAs	**:** Catecholamines
CIP	**:** Critically Ill Patients
CRF	**:** Corticotrophin-Releasing Factor
DM	**:** Diabetes Mellitus
FFA	**:** Free Fatty Acid
GLUT	**:** Glucose Transporter
HPA	**:** Hypothalamic–Pituitary–Adrenal
ICU	**:** Intensive Care Unit
IKK	**:** Inhibitor κB Kinase
IL	**:** Interleukin
IRS	**:** Insulin Receptor Substrate
JNK C-Jun	**:** N-Terminal Kinase
NF	**:** Nuclear Factor
NO	**:** Nitric Oxide
PEPCK	**:** Phosphoenolpyruvate Carboxykinase
PEPCK	**:** Phosphoenolpyruvate Carboxykinase
PI3K	**:** phosphatidylinositol 3 kinase
ROS	**:** Reactive Oxygen Species
TNF	**:** Tumor Necrosis Factor
TPN	**:** Total Parenteral Nutrition

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Abstract

Since early 1960s, blood lactate concentrations have been used widely as a marker of altered tissue perfusion in critically ill patients. Hyperlactatemia is a hallmark characteristic of shock states and the degree of increase in lactate concentrations is directly related to the severity of the shock state and to mortality rates. On the other hand, both hyperglycemia and hypoglycemia in the intensive care unit (ICU) patient have long been associated with increased morbidity and mortality. The worsened outcome from hyperglycemia occurs not only in patients with diabetes, but also in non-diabetics when enhanced glycogenolysis and gluconeogenesis combined with impaired glucose consumption and impaired glycogen production lead to stress-induced hyperglycemia. Recently, a growing body of evidence has suggested that abnormal combined lactate and glucose levels may provide an early indication of organ dysfunction in ICU patients. Therefore, we conducted the present retrospective study in order to investigate whether the risks of morbidities and mortality are higher in ICU patients with hyperlactatemia and higher/lower glycemic level. In the present study, we included 100 cases that had an ICU stay of at least 12 hours. The mean age of the included patients was 46.2 ±15.4 year; while the majority of them were males (58%) and smokers (62%). Notably, the mortality rate in the present study was 37%. In the present study, the median lactate level decreased significantly from 2.3 (1.3-5) mg/dL at first six hours of ICU admission to reach 1.4 (0.9–3.8) mg/dL after 24 hours ($p < 0.001$). Forty-eight perent of the patients had hyperlactatemia at admission. Our analysis showed that the serum lactate level was significantly higher in dead patients than the patients who survived ($p < 0.001$). Moreover, the proportion of dead patients were significantly higher in hyperlactatemia group than normal lactate level at admission group ($p < 0.001$). On the other hand, our analysis showed thatthe random blood sugar level was not significantly different between dead patients and the patients who survived ($p = 0.58$). However, a statistically significant higher proportion of patients with hyperglycemia were dead compared to patients with normal glycaemia at admission ($p = 0.007$). With regard to our primary outcome, 40% of the patients in the present study had combined hyperlactatemia and hyperglycemia at admission; while 11% had combined hyperlactatemia and hypoglycemia. Notably, statistically signifcant higher proportions of patients in combined hyperlactatemia and hyperglycemia required mechanical ventilation ($p = 0.049$), had higher APACHE IV ($p = 0.026$), longer length of hospital stay ($p = 0.013$), and higher mortalitly than patients with normal lactate and normal blood glucose levels. In conclusion, patients admitted to ICU with combine hyperlactatemia and hyperglycemia are at increased risk of adverse outcomes than patients without this combination. Our study showed that patients with combine hyperlactatemia and hyperglycemia were more likely to require mechanical ventilation, had higher APACHE IV, and longer length of hospital stay than patients with normal lactate and normal blood glucose levels. [Bahaa Elden Eweas Hassan, Dina Salah Elden Mouhamed, Mai Mohsen Abdlaziz Gadallah, Ahmed Ramadn Abdlaziz Abdlgawad. The association of early combined lactate and glucose levels and hospital mortality in critically ill patients. *J Am Sci* 2019;15(6):17-26]. ISSN 1545-1003 (print); ISSN 2375-7264 (online). http://www.jofamericanscience.org. 3. doi:10.7537/marsjas150619.03.

Keywords: association; lactate; glucose; level; mortality; ill; patient

Introduction

Derangements of lactate and glucose levels are common in critically ill Patients. In the routinely available laboratory measurements, lactate has the strongest relation with outcome in a broad variety of clinical settings. As a result, it is increasingly used to monitor the effectiveness of instituted therapy. Since lactate and glucose monitoring has steadily gained popularity, optimal understanding of changes in glyco-metabolism, may improve interpretation of acute clinical Change. Lactate and glucose are linked through both glycolysis and gluconeogenesis and both pathways are part of the Cori cycle. Gluconeogenesis which is performed by the liver and the kidney recycles circulating lactate into glucose. Mild hypoglycemia can be the result of dysfunction of the gluconeogenetic organs and it has been associated with impaired renal and liver function which affects outcome **(Vincent et al., 2016).**

Most frequently, the stress reaction that accompanies acute critical illness directly induces both hyperlactatemia and hyperglycemia. Thus hyperlactatemia without hyperglycemia might constitute already an abnormal response in the face of stress. Therefore we hypothesized that the combination of an elevated lactate with even a 'normal' glucose, might be associated with an increased incidence of renal or liver

dysfunction and hospital mortality. Most observational and retrospective studies have reported that hyperglycemia in patients with severe disease, is associated with an increased risk of complications, longer ICU stay and higher mortality rates. Hyperlactatemia is common among patients requiring critical care, and lactate levels and their trend may be reliable markers of illness severity and mortality. Abnormal combined lactate and glucose measurements may provide an early indication of organ dysfunction. In critically ill patients a 'normal' glucose with an elevated lactate should not be considered desirable, as this combination is related with increased mortality **(Pedro et al., 2017).**

Aim of the Work

This study aims to clarify the role of early measurement of glucose & lactate level and its role in mortality & morbidities in critically ill patients. It is confirming that Increased organ dysfunction is found more in patients with hyperlactatemia with higher & or lower glycemic level and it is less with mid glycemic control.

It also clarifies that Aggressive control of hyperglycemia is associated with incidence of hypoglycemia and therefore increasing the mortality rates. It aims to prove that Hospital mortality and organ dysfunction improved with better lactate monitoring& glycemic control.

Lactate Production and Removal

The lactate production every day in resting humans is estimated as 20 mmol/kg and Production is primarily from highly glycolytic tissues like skeletal muscles (**Shigeki et al., 2016).**

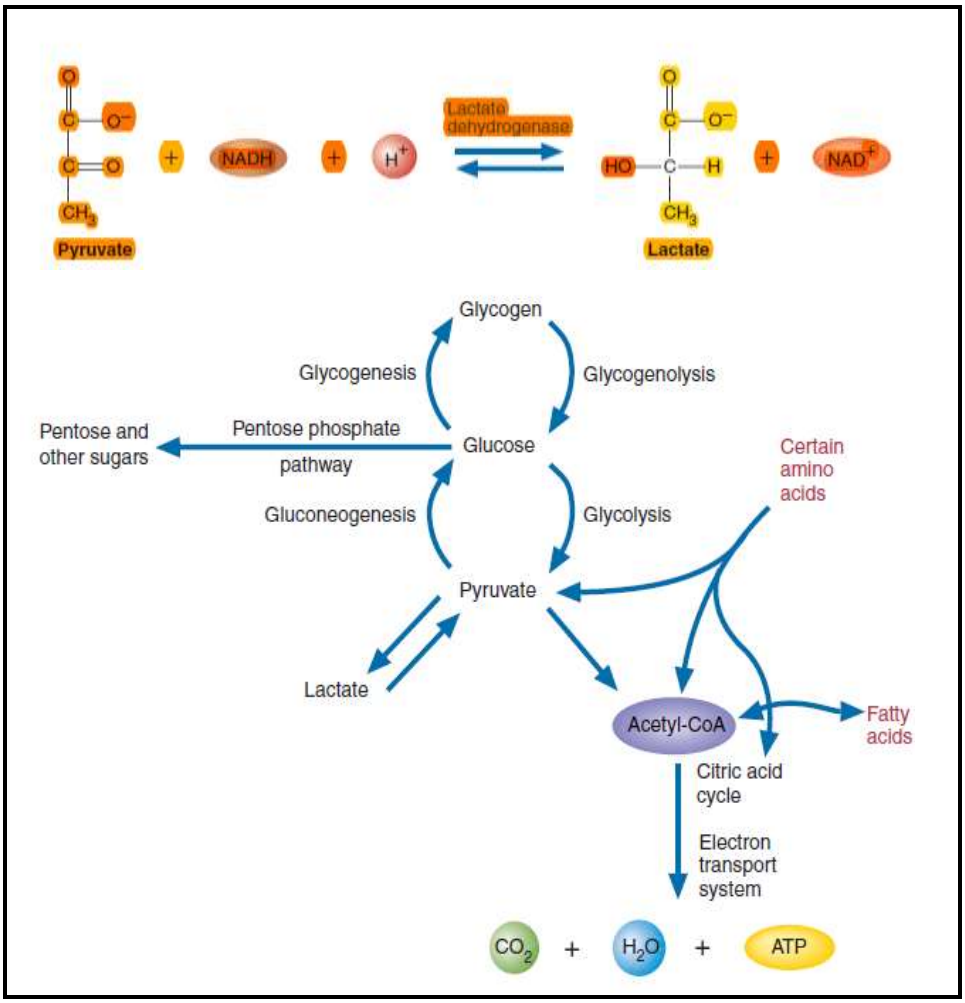

Figure (1): Pyruvate + NADH + H+⇌ lactate + NAD and Glycolysis in the absence and presence of oxygen ***(Bakker et al., 2016).***

Pyruvate is generated in large amount by anaerobic glycolysis. The redox-coupled inter conversion of pyruvate and lactate, occur in the cytosol and is catalyzed by lactate dehydrogenase. The blood lactate: pyruvate ratio is maintained at approximately 10:1; therefore, any condition that increase pyruvate generation will increase lactate generation (Figure 2).

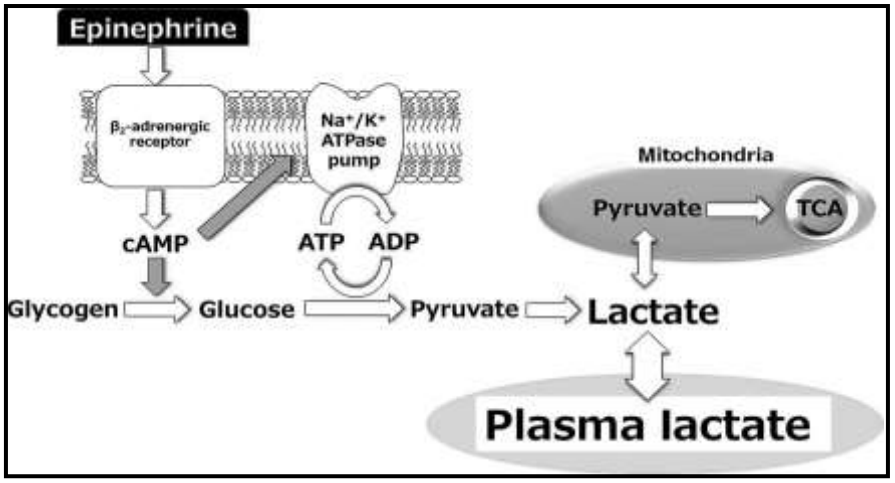

Figure (2): Epinephrine-induced lactate production **(Shigeki et al., 2016).**

Lactate can be metabolized by the liver and the kidneys either through direct oxidation or as a source of glucose. The liver accounts for up to 70% of whole body lactate clearance. Under normal conditions, the generation and consumption of lactate are equivalent, which results in a stable concentration of lactate in the blood. Lactate is reconverted to pyruvate and it is metabolized in the liver, kidney, and other tissues through the Cori cycle, that generates glucose and consumes adenosine

triphosphate (ATP) (gluconeogenesis) (Figure 3). Lactate is also metabolized through the tricarboxylic acid cycle and oxidative phosphorylation in the liver, kidney, muscle, heart, brain, and other tissues, generating ATP, when pyruvate is oxidized to carbon dioxide and water. Half of lactate is metabolized through oxidation at rest and 75–80% during exercise. In contrast, lactate production by muscle and other tissues is coupled with its conversion to glucose **(Shigeki et al., 2016).**

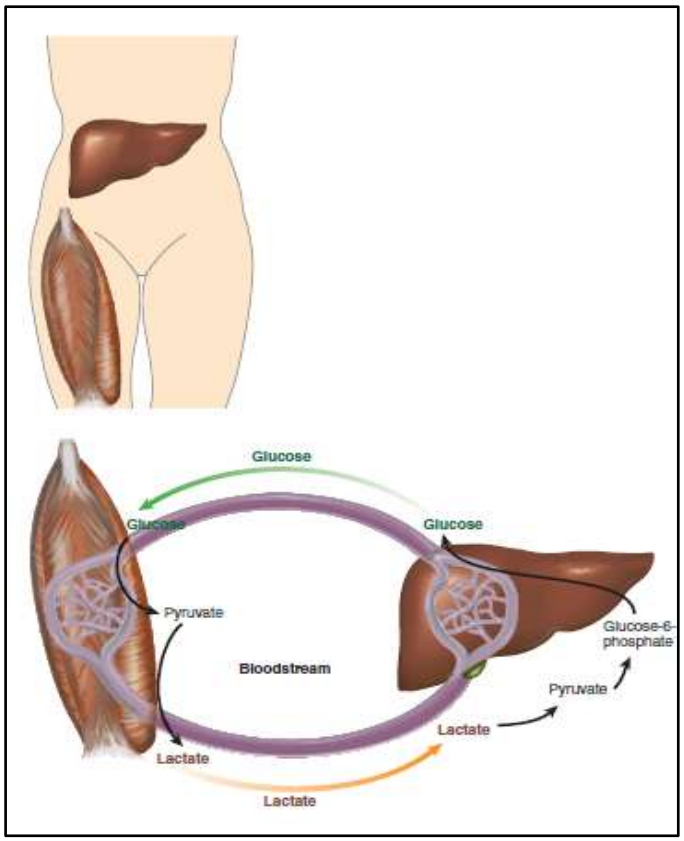

Figure (3): The Cori Cycle **(Bakker et al., 2000).**

During strenuous exercise, lactate is produced anaerobically in muscle cells. After passing through blood to the liver, lactate is converted to glucose by gluconeogenesis. Lactate is an important precursor of gluconeogenesis and a key source of glucose. Under stress conditions, lactate has been suggested to act as a biofuel, which eliminates blood glucose use and provides additional glucose. Therefore, hyperlactatemia may indicate a protective response to stress under critical conditions **(Miller et al., 2002).**

Hyperlactatemia and its clearance in critically ill patients

The mechanism of hyperlactatemia in critical illness is multifactorial and associated with factors, beyond tissue hypoxia/hypo perfusion. Lactic acidosis refractory to standard resuscitation is frequently caused by increased anaerobic glycolysis in skeletal muscle instead of aerobic glycolysis from hypo perfusion. Continued resuscitation attempts targeting lactate levels, may lead to unnecessary blood transfusion and use of inotropic agents. It was also suggested that resuscitation efforts to normalize lactate for hyperlactatemia in the later phase of sepsis could be flawed and potentially harmful. However, the data supporting the clinical utility of lactate as a marker of early sepsis recovery are robust. In a recently revised sepsis definition, serum lactate level >2 mmol/L (18 mg/dL),