بسم الله الرحمن الرحيم

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بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

ملاحظات: ....

Effect of Glycemic Control on Sepsis in Critically Ill Diabetic Patients: a Prospective Cohort Study

Thesis

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in **General Intensive Care Unit**

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Michael Mamdouh Anwar

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List of Abbreviations

Abb.	Full term

aBNST ..... *Anterior bed nucleus of the striaterminalis*
ADA ..... *American Diabetes Association*
AP ..... *Arterial pressure*
APCr ..... *Activated protein C*
AR ..... *Androgen receptor*
ASL ..... *Airway surface liquid*
BAT ..... *Brown adipose tissue*
BG ..... *Blood glucose*
CCK ..... *Cholecystokinin*
CD36 ..... *Cluster of differentiation 36*
CRP ..... *C-reactive protein*
CVP ..... *Central venous pressure*
DIGAMI ..... *Diabetes Insulin Glucose in Acute Myocardial Infarction*
ER ..... *Estrogen receptors*
ESI ..... *Electrospray ionization*
GIGD ..... *Gastro intestinally induced glucose disposal*
GIK ..... *Glucose insulin potassium*
GIP ..... *Glucose insulin polypeptide*
GLP-1 ..... *Glucagon like peptide-1*
GLUT ..... *Glucose transporter*
GLUT2 ..... *Glucose transporter two*
GPER ..... *G-protein coupled ER*
HbA1c ..... *Hemoglobin*
HHS ..... *Hyperglycemic hyperosmolar state*
ICU ..... *Intensive care unit*
IL ..... *Interleukin*
LPBN ..... *Lateral Para brachial nucleus cholecystokinin*
MALDI ..... *Matrix assisted laser desorption Ionization*

List of Abbreviations (cont...)

Abb.	Full term
MAP	*Mean arterial pressure*
MS	*Mass spectrometry*
NAT	*Nucleic acid testing*
NICE	*Normoglycemia in Intensive Care Evaluation*
PCR	*Polymerase chain reaction*
PCT	*Procalcitonin*
PiCOO	*Pulse contour cardiac output*
RBG	*Random blood glucose*
ScvO2	*Venous oxyhemoglobin saturation*
SERCA	*Sarcoplasmic reticulum Ca2+ATPase pump*
SF1	*steroidogenic-factor 1*
SNS	*Sympathetic nervous system*
SSI	*Sliding scale of insulin*
SUGAR	*Survival Using Glucose Algorithm Regulation*
SvcO 2	*Central venous oxyhemoglobin saturation,*
T2D	*Two diabetes*
THs	*Thyroid hormones*
TNF- α	*Tumor necrosis factor alpha*
TOF	*Time-of-flight*
TT	*Transthoracic*
VMH	*Ventromedial nucleus of the hypothalamus*
WAT	*White adipose tissue*
ΔpCO 2	*Venous to arterial pCO2 difference*

INTRODUCTION

Hyperglycemia is common and often multifactorial in critically ill patients. Severe hyperglycemia can result in endothelial dysfunction, cytokine release, platelet activation, mitochondrial dysfunction and electrolyte and acid base disturbances ***(Dungan et al., 2009)*** and has been associated with an adverse outcome in a variety of settings in patients without a history of diabetes; this association has not been demonstrated in diabetes patients ***(Stegentga et al., 2010).***

Intervention directed at reducing blood glucose (BG) levels has resulted in improved outcomes in some, but not all, studies ***(De la Rosa et al., 2008)***. Several clinical trials in critically ill patients have reported no reduction in mortality from intensive treatment targeting near- euglycemia versus conventional management targeting BG 180 mg/dl (10.0 mmol/l).

Of considerable concern are reports of harm, with higher rates of severe hypoglycemia and even increased mortality ***(Nice-Sugar Study Investigators, 2009).*** As a single episode of severe hypoglycemia was independently associated with increased risk of mortality. Safe implementation of tight glycemic control requires appropriate monitoring to reduce the risk of this complication ***(Krinsley and Grover, 2007).***

Aim of the Work

Aim is to evaluate the outcome of glycemic control in critically ill diabetic patients.

Chapter 1

GLUCOSE METABOLISM

Glucose is an important metabolic substrate in mammalian cells; it can be metabolized by series of reactions that extract energy from it or convert it into other important products as free fatty acids, amino acids and glycogen.

(1) **Glycolysis**: it's the first step of complete oxidation pathway in the cell cytoplasm, whatever anaerobically or aerobically in this process the six carbon glucose molecule is cleaved into two molecules of the three carbon compound pyruvate, two Adenosine triphosphate (ATP) and two Nicotinamide adenine dinucleotide (NADHH) that act as an electron acceptor cofactor which is available in limited amounts and should be re oxidized to NAD for continuation of glycolysis process (***Szablewski, 2011).***

(2) **Oxidative decarboxylation**: under aerobic condition of glucose metabolism in mitochondria one pyruvate molecule can be oxidized into two molecules of acetyl co enzyme A and two NADHH, releasing its carboxyl group as two Co2 molecules (***Szablewski, 2011).***

(3) **Krebs cycle**: in mitochondrial matrix acetyl co enzyme A is oxidized ultimately to Co2, compounds that produced in this reactions can be used as a building block for important products as fatty acids, steroids, cholesterol, amino acids, purines and pyrimidines while Krebs cycle does produce Co2 it doesn't produce

significant chemical energy in the form of ATP directly but produce NADHH (Nicotinamide adenine dinucleotide), FADH2 (Flavin adenine dinucleotide) that by respiratory cycle located in inner mitochondrial membrane - what's called electron transport chain – they can be converted into a large quantity of ATP (Adenosine triphosphate). In respiratory cycle one NADHH produce three ATP and one FADH2 give two ATP where oxygen is the final electron acceptor that combines with proton forming water **(*Szablewski, 2011)***.

(4) **Lactate metabolism**: under anaerobic conditions pyruvate produced from glycolysis is reduced to lactate by the cofactor NADHH keeping available amount of oxidized NAD for further glycolysis but accumulation of lactate in the cell decrease its PH that interfere with the cellular function hence the need for good handling of lactate molecule by two mechanisms (***Szablewski, 2011):***

A) Lactate dehydrogenase enzyme: the enzyme oxidize lactate to pyruvate that may be oxidized under aerobic condition.

B) Gluconeogenesis: lactate formed in skeletal muscle and red blood corpuscles is released into the blood stream and handled by the liver cells that convert it into glucose which can be released into blood stream and taken by skeletal muscles what's called the Cori cycle which need four molecules of ATP to convert lactate produced by glycolysis into glucose but glycolysis give only two

molecules of ATP that's why Cori cycle can't be sustained indefinitely. Although Cori cycle is net consumer energy its important in maintaining circulating glucose concentration in the blood stream even in absence of dietary intake.

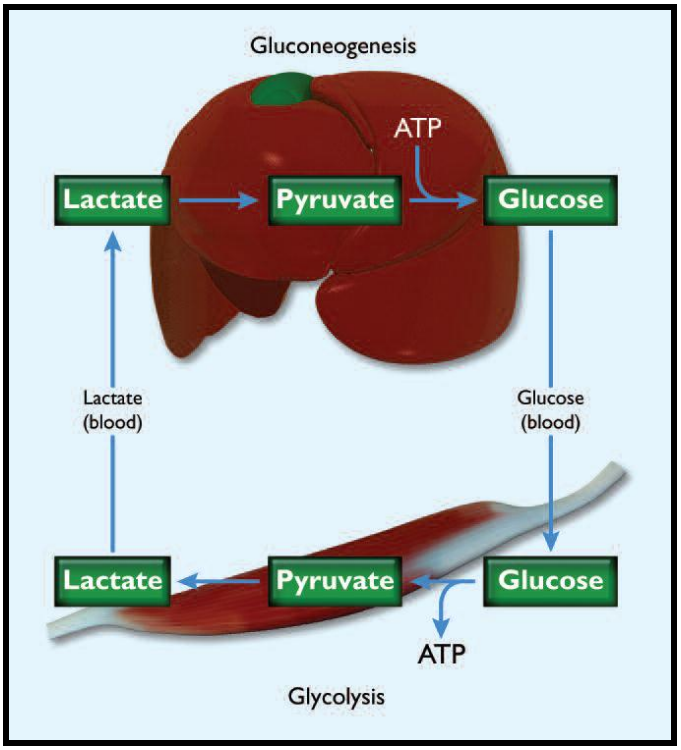

Figure (1): The Cori cycle. Anaerobic glycolysis can provide short-term energy needs in muscle. The by-product, lactate, diffuses into the blood and is taken up by the liver. The liver uses the enzyme lactate dehydrogenase to convert lactate to pyruvate. Pyruvate is then converted back to glucose via gluconeogenesis ***(Knieriem et al., 2007).***

(5) **Glycogenesis**: its process of storage of glucose by forming glycogen in liver activated by insulin hormone or in muscle during rest after Cori cycle (***Szablewski, 2011).***

(6) **Glycogenolysis**: in response to falling blood glucose level, the glycogen molecules - the storage form of glucose in liver and muscle – are broken down into glucose six phosphate that can be released into blood stream from hepatocytes that uniquely have glucose six phosphatase enzyme but muscle cells don't have this enzyme; keeping released glucose six phosphate from muscular glycogen trapped for its own consumption only (***Agius, 2015).***

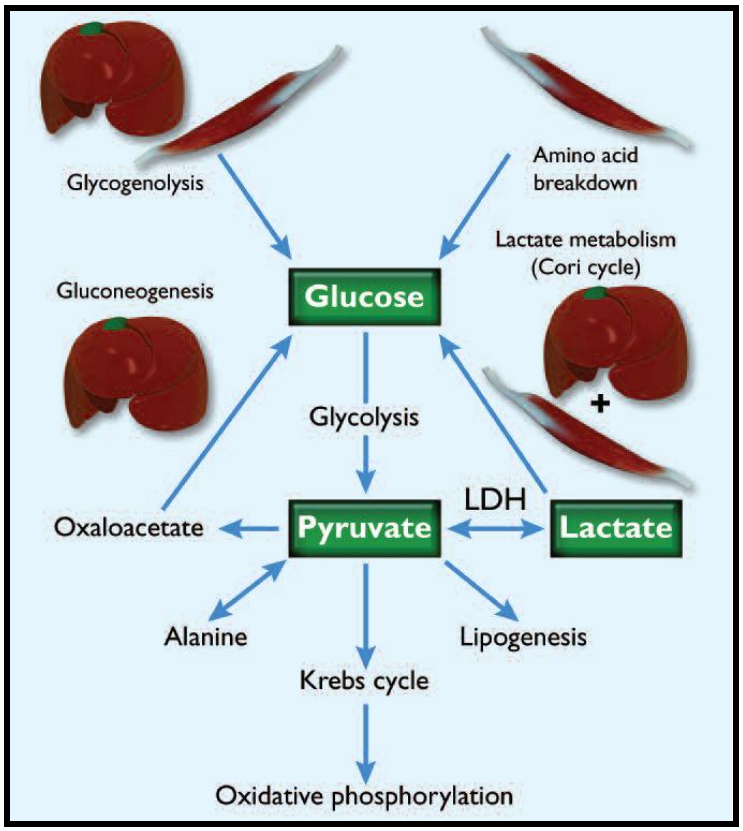

Figure (2): Glycolysis is the central energy pathway in most living organisms**.** Sources of bodily glucose include digestion of carbohydrates, glycogenolysis, gluconeogenesis, amino acid breakdown, and lactate