Introduction

The critically ill patient in intensive care often has to face significant metabolic alterations caused directly by the illness or secondary by complications (i.e. infections, organ failure or sepsis). Situations of rapidly evolving altered metabolism are maintained by or can trigger complex hormonal reactions which in turn promote further metabolic derangements. The metabolic support of the critically ill patient is a relatively new target of active research and little is yet known about the effects of critical illness on metabolism (**Palmer and Bessy, 2011**).

The critically ill patient exhibits a well defined endocrine and metabolic adaptive response to stressor agents, characterized by incremented energy requirement, accelerated whole-body proteolysis (hypercatabolism), and lipolysis. These phenomena occur in the acute stage, which is also characterized by hyperglycemia, typically accompanied by a hyperdynamic cardiovascular reaction manifested by high cardiac output, increased oxygen consumption, high body temperature, and decrease peripheral vascular resistance (**José et al., 2000**).

Metabolic disorders and endocrine changes are common and relevant in critically ill patients. Thereby, endocrinopathies, electrolyte or metabolic derangements may either pre-exist or develop, and may lead to significant morbidity and moratality. The homeostatic corrections which have emerged in the course of human evolution to cope with the catastrophic events during critical illness involve complex multisystem affections, of which the endocrine contribution is an integral component. That disturbances in glucose and cortisol homestasis during critical illness are two controversially debated topics in the current literature. The term "hormokine" encompasses the cytokine like behavior of

hormones during inflammation and infections in critical illness (**Muller, 2007**).

Pathoghysiology, consequences and management of hyperglycemia during critical illness is an important clinical issue. Uncontrolled hyperglycemia in this setting is associated with a variety of adverse events, including morbidity and mortality, so that effective management of hyperglycemia in critically ill patients has been a major topic of discussion since a landmark study demonstrated a significant reduction in mortality and morbidity in surgical patients who were treated with an intensive regimen to control blood glucose (**Ravindra and Mehta, 2007**).

Thyroid hormones play an important role in the adaptation of metabolic function to stress and critical illness. In hospitalized patients, thyroid hormone alterations are very common, particularly in those of increased age, or critical illness. However, they are rarely the primary cause of admission to the intensive care unit (**ICU**) (**Iglesias et al., 2009**). So nonthyroidal illness syndrome, that is also known as the low T3 syndrome or euthyroid sick syndrome, describes a condition characterized by abnormal thyroid function tests encountered in patients with acute or chronic systemic illness (**Economidou and Douka, 2011**).

In the critical ill patients malnutrition may be preexistent, manifest itself upon admission or develop as a result of the hypercatabolic state in these patients. So that the critically ill patients invariably require nutritional intervention. Traditionally, enteral nutrition has not been widely employed in these patient populations. This is due in part to the success of present-day parenteral nutrition in terms of cost, complications, gut mucosal maintenance, and metabolic and immune function (**Maica and Schweigert, 2008**).

Enteral nutrition (EN) via tube feeding is today the preferred way of feeding in the critically ill patient and an important mean of counteracting for the catabolic state induced by severe diseases, focusing particularly on those who develop a severe inflammatory response (**Kreymann et al., 2006**).

Aim of the Work

The aim of the essay is to provide a review of the pathophysiology of the metabolic alterations and metabolic responses in critically ill patients and its effect on the outcome of these patients (considerations and management).

Physiology and pathophysiology of metabolism in critically ill patients

Glucose Metabolism;

The final products of carbohydrate digestion in the alimentary tract are almost entirely glucose, fructose, and galactose—with glucose representing, on average, about 80 percent of these. After absorption from the intestinal tract, much of the fructose and almost all the galactose are rapidly converted into glucose in the liver. Therefore, little fructose and galactose are present in the circulating blood **(Guyton and Hall (A), 2006)**.

Before glucose can be used by the body's tissue cells, it must be transported through the tissue cell membrane into the cellular cytoplasm. However, glucose cannot easily diffuse through the pores of the cell membrane because the maximum molecular weight of particles that can diffuse readily is about 100, and glucose has a molecular weight of 180. Yet glucose does pass to the interior of the cells with a reasonable degree of freedom by the mechanism of facilitated diffusion. Immediately on entry into the cells, glucose combines with a phosphate. This phosphorylation is promoted mainly by the enzyme glucokinase in the liver and by Hexokinase in most other cells **(Guyton and Hall (A), 2006)**.

Plasma glucose concentration is a function of the rate of glucose entering the circulation (glucose appearance) balanced by the rate of glucose removal from the circulation (glucose disappearance). Circulating glucose is derived from three sources: intestinal absorption during the fed state, glycogenolysis, and gluconeogenesis. The major determinant of how quickly glucose appears in the circulation during the fed state is the rate of gastric emptying. Other sources of

circulating glucose are derived chiefly from hepatic processes: glycogenolysis, the breakdown of glycogen, the polymerized storage form of glucose; and gluconeogenesis, the formation of glucose primarily from lactate and amino acids during the fasting state **(Stephen et al., 2004).**

After absorption into a cell, glucose can be used immediately for release of energy to the cell, or it can be stored in the form of glycogen, which is a large polymer of glucose.all cells of the body are capable of storing at least some glycogen, but certain cells can store large amounts, especially liver cells, which can store up to 5 to 8 percent of their weight as glycogen, and muscle cells, which can store up to 1 to 3 percent glycogen. The glycogen molecules can be polymerized to almost any molecular Weight, with the average molecular weight being 5 million or greater; most of the glycogen precipitates in the form of solid granules **(Ferrer et al., 2003).**

Glycogenolysis means the breakdown of the cell's stored glycogen to reform glucose in the cells. The glucose can then be used to provide energy. Glycogenolysis does not occur by reversal of the same chemical reactions that form glycogen; instead, each succeeding glucose molecule on each branch of the glycogen polymer is split away by phosphorylation, catalyzed by the enzyme phosphorylase. Under resting conditions, the phosphorylase is in an inactive form, so that glycogen will remain stored. When it is necessary to reform glucose from glycogen, the phosphorylase must first be activated. This can be accomplished by two hormones, epinephrine and glucagon **(Jiang and Zhang, 2003).**

When the body's stores of carbohydrates decrease below normal, moderate quantities of glucose can be formed from amino acids and the glycerol portion of fat. This process is called Gluconeogenesis. Gluconeogenesis is

especially important in preventing an excessive reduction in the blood glucose concentration during fasting. Glucose is the primary substrate for energy in tissues such as the brain and the red blood cells, and adequate amounts of glucose must be present in the blood for several hours between meals **(Lam et al., 2003)**.

The liver plays a key role in maintaining blood glucose levels during fasting by converting its stored glycogen to glucose (glycogenolysis) and by synthesizing glucose, mainly from lactate and aminoacids (Gluconeogenesis). Approximately 25 percent of the liver's glucose production during fasting is from Gluconeogenesis, helping to provide a steady supply of glucose to the brain **(Roden and Bernoider, 2003).**

During prolonged fasting, the kidneys also synthesize considerable amounts of glucose from amino acids and other precursors. About 60 per cent of the amino acids in the body proteins can be converted easily into carbohydrates; the remaining 40 percent have chemical configurations that make this difficult or impossible **(Lam et al., 2003)**.

Because complete oxidation of 1 gram-molecule of glucose releases 686, 000 calories of energy and only 12, 000 calories of energy are required to form 1gram-molecule of ATP, energy would be wasted if glucose were decomposed all at once into water and carbon dioxide while forming only a single ATP molecule. Fortunately, all cells of the body contain special protein enzymes that cause the glucose molecule to split a little at a time in many successive steps, so that its energy is released in small packets to form one molecule of ATP at a time, forming a total of 38 moles of ATP for each mole of glucose metabolized by the cells **(Guyton and Hall (A), 2006)**.

Glucose Metabolism in Critically Ill Patients:

Critical illness affects millions of people worldwide and is associated with a high risk of organ failure and death or an adverse outcome with persistent physical or cognitive deficits. Spontaneous hyperglycemia is common in critically ill patients and is associated with an adverse outcome compared to normoglycemia **(Nielsen et al., 2013).**

A characteristic of critical illness is the so-called 'diabetes of stress' with hyperglycemia and insulin resistance. Hepatic gluconeogenesis (from amino acids and lactate) increases mainly due to the action of catabolic hormones such as glucagon, epinephrine, and cortisol. In addition, the normal suppressive action of exogenous glucose and insulin on hepatic gluconeogenesis is decreased. Peripheral glucose utilization in insulin-dependent tissues (muscle and fat) is also decreased **(Michael et al., 2008).**

There are many types of stress associated with hospitalization and illness. There are psychological, emotional and physical stressors. It is important to distinguish which type of stress contributes to the hyper metabolic state associated with critical illness and define stress **(Laura, 2009).**

Stressors can be further categorized as ether cognitive and non-cognitive stress. Cognitive stressors are usually emotions such as fear, depression or bereavement. Non cognitive stressors can be physical such as injury, surgery infections, or pain. The stress response is the body's uniform reaction to all types of stressors.Stress hyperglycemia is one of the physiological components of the stress response caused by cognitive and non cognitive stressors associated with hospitalization and illness **(Mechanick, 2006))**.

Stress and critical illness has numerous effects on physiology. The stress response changes endocrine secretions and causes many metabolic changes. The deviation from

normal resting glucose metabolism combined with decreased insulin secretion and peripheral insulin resistance during critical illness ultimately leads to stress hyperglycemia. As a part of the physiological component of the stress response is changes of hormones secretions in the body. An increase in counter regulatory hormones is the major change that occurs during stress **(Laura, 2009)**

Counter regulatory hormones are hormones that oppose the action of insulin. The increase in Counter regulatory hormones during stress has many metabolic repercussions.Norepinephrine, epinephrine, growth hormone, cortisol, and glucagon induce gluconeogenesis, glycogenolysis causing increase hepatic glucose production and decrease peripheral glucose uptake this shift in metabolic activity is driven by fat and protein metabolism, which provide the necessary precursors for gluconeogenesis. Cortisol promotes proteolysis to provide amino acids such as alanine for Gluconeogenesis. Epinephrine and nor epinephrine induce the breakdown of fats, providing glycerol for Gluconeogenesis.Hepatic and skeletal muscle glycogenolysis is also increased by the presence of epinephrine and norepinephrine **(Gerhart and parbhoo, 2006).**

Protein metabolism:

Nitrogen metabolism is no less important than carbohydrate and lipid metabolism. About three quarters of the body solids are proteins. Proteins make up the structural tissue for muscles and tendons, transport oxygen on hemoglobin, catalyze all biochemical reactions as enzymes, and regulate reactions as hormones. Our bodies must be able to synthesize many proteins, amino acids, and other nonprotein nitrogen containing compounds needed for growth, replacement, and repair. Proteins in excess are used to supply energy or build reserves of glucose, glycogen, or lipids **(Charles, 2003)**.

Ten of the amino acids normally present in animal proteins can be synthesized in the cells, whereas the other 10 either cannot be synthesized or are synthesized in quantities too small to supply the body's needs. This second group of amino acids that cannot be synthesized is called the essential amino acids. Use of the word" essential" does not mean that the other 10 "nonessential" amino acids are not required for the formation of proteins, but only that the others are not essential in the diet because they can be synthesized in the body. Synthesis of the nonessential amino acids depends mainly on the formation of appropriate a-keto acids which are the precursors of the respective amino acids. For instance, pyruvic acid, which is formed in large quantities during the glycolytic breakdown of glucose, is the keto acid precursor of the amino acid alanine.Then, by the process of transamination, an amino radical is transferred to the a-keto acid, and the ketooxygen is transferred to the donor of the amino radical **(Guyton and Hall (B), 2006)**.

The products of protein digestion and absorption in the gastrointestinal tract are almost entirely amino acids; only rarely are polypeptides or whole protein molecules absorbed from the digestive tract into the blood. Immediately after a meal, the amino acid concentration in a person's blood rises, but the increase is usually only a few milligrams per deciliter, for two reasons: First, protein digestion and absorption are usually extended over 2 to 3 hours, which allows only small quantities of amino acids to be absorbed at a time. Second, after entering the blood, the excess amino acids are absorbed within 5 to 10 minutes by cells throughout the body, especially by the liver. Therefore, almost never do large concentrations of amino acids accumulate in the blood and tissue fluids. Nevertheless, the turnover rate of the amino acids is so rapid that many grams of proteins can be carried from one part of the body to another in the form of amino acids each hour **(Daniel, 2004).**

The molecules of all the amino acids are much too large to diffuse readily through the pores of the cell membranes. Therefore, significant quantities of amino acids can move either inward or outward through the membranes only by facilitated transport or active transport using carrier mechanisms **(Deves and Boyd, 1998)**.

Almost immediately after entry into tissue cells, amino acids combine with one another by peptide linkages, under the direction of the cell's messenger RNA and ribosomal system, to form cellular proteins. Therefore, the concentration of free amino acids inside the cells usually remains low. Thus, storage of large quantities of free amino acids does not occur in the cells; instead, they are stored mainly in the form of actual proteins. But many of these intracellular proteins can be rapidly decomposed again into amino acids under the influence of intracellular lysosomal digestive enzymes; these amino acids can then be transported back out of the cell into the blood. Special exceptions to this reversal process are the proteins in the chromosomes of the nucleus and the structural proteins such as collagen and muscle contractile proteins; these proteins do not participate significantly in this reverse digestion and transport back out of the cells. Some tissues of the body participate in the storage of amino acids to a greater extent than others. For instance, the liver, which is a large organ and has special systems for processing amino acids, can store large quantities of rapidly exchangeable proteins; this is also true to a lesser extent of the kidneys and the intestinal mucosa **(Jans and Habner, 1996).**

Each particular type of cell has an upper limit with regard to the amount of proteins it can store. After all the cells have reached their limits, the excess amino acids still in the circulation are degraded into other products and used for energy, , or they are converted to fat or glycogen and stored in these forms.. This degradation occurs almost entirely in

the liver, and it begins with deamination, which means removal of the amino groups from the amino acids. This occurs mainly by transamination, which means transfer of the amino group to some acceptor substance, which is the reverse of the transamination explained earlier in relation to the synthesis of amino acids. Essentially all urea formed in the human body is synthesized in the liver. In the absence of the liver or in serious liver disease, ammonia accumulates in the blood. This is extremely toxic, especially to the brain, often leading to a state called hepatic coma. The stages in the formation of urea are essentially the following: After its formation, the urea diffuses from the liver cells into the body fluids and is excreted by the kidneys **(Moriwaki et al., 2004).**

Once amino acids have been deaminated, the resulting ketoacids can, in most instances, be oxidized to release energy for metabolic purposes. This usually involves two successive processes: (1) the ketoacid is changed into an appropriate chemical substance that can enter the citric acid cycle, and (2) this substance is degraded by the cycle and used for energy in the same manner that acetyl coenzyme A (acetyl-CoA) derived from carbohydrate and lipid metabolism is used. In general, the amount of adenosine triphosphate (ATP) formed for each gram of protein that is oxidized is slightly less than that formed for each gram of glucose oxidized **(Guyton and Hall (B), 2006)**.

Regulation of protein metabolism:

Protein metabolism in health and during disease is predominantly regulated by substrate availability and hormonal concentrations while during disease the pro-Inflammatory mediators also play important roles **(Van Waardenburg, 2008).**

A-Plasma amino acid concentrations

An increase in the plasma concentrations of essential amino acids is the most important factor stimulating muscle protein synthesis (muscle PS). Although muscle PS takes place in the cytoplasm or endoplasmatic reticulum, extracellular amino acid concentrations serve as signals to activate protein synthesis although it is not known how amino acid availability is sensed by the cell. Once synthesis is activated this results in increased rate of inward transport of amino acids. Nonessential amino acids are not needed for the stimulation of muscle PS. The response to increased amino acid availability however may be time dependent. During a continuous intravenous amino acid infusion the rate of muscle PS has been shown to rapidly rise but to decrease again after 2 hours (**Bohe et al., 2001).**

During critical illness the plasma and tissue concentration of most amino acids are decreased. This is especially true for the intracellular amino acid concentrations but also the large majority of plasma amino acids show a decline in concentration. The decrease in plasma amino acid concentrations occurs early during critical illness. In general it is believed that these changes are a reflection of starvation due to limited nutritional protein supply, increased hepatic utilization for acute phase protein synthesis, Gluconeogenesis and oxidation for energy supply and protein synthesis in immune cells. These changes persist as long as the infection persists and resolve during recovery **(van Waardenburg, 2008).**

B-Energy intake:

Energy intake has an important influence on protein metabolism. When energy intake is lower than energy expenditure (negative energy balance) either due to an inadequate dietary intake or an increased energy expenditure,

catabolism of body energy stores occurs including increased breakdown of muscle protein **(Biolo et al., 2008).** After deamination or transamination the carbon skeletons of amino acids are then used to meet energy needs. Carbohydrates and fat alone have no direct effect on muscle protein synthesis but exert important influences on protein metabolism by their energy content and their hormonal effects for instance on glucagon and especially insulin secretion **(Millward, 2004).**

C-Hormonal Regulation of Protein Metabolism:

1- Growth Hormone Increases the Synthesis of Cellular Proteins:

Growth hormone causes the tissue proteins to increase.The precise mechanism by which this occurs is not known, but it is believed to result mainly from increased transport of amino acids through the cell membranes or acceleration of the DNA and RNA transcription and translation processes for protein synthesis **(Pencharz and Ball, 2004)**.

2-Insulin Is Necessary for Protein Synthesis:

Total lack of insulin reduces protein synthesis to almost zero. The mechanism by which this occurs is also unknown, but insulin does accelerate the transport of some amino acids into cells, which could be the stimulus to protein synthesis. Also, insulin increases the availability of glucose to the cells, so that the need for amino acids for energy is correspondingly reduced **(Prod'homme et al., 2004).**

3- Glucocorticoids Increase Breakdown of Most Tissue Proteins:

The glucocorticoids secreted by the adrenal cortex decrease the quantity of protein in most tissues while increasing the amino acid concentration in the plasma, as

well as increasing both liver proteins and plasma proteins. It is believed that the glucocorticoids act by increasing the rate of breakdown of extrahepatic proteins, thereby making increased quantities of amino acids available in the body fluids. This supposedly allows the liver to synthesize increased quantities of hepatic cellular proteins and plasma proteins **(Kuhn, 2002)**.

4-Testosterone Increases Protein Deposition in Tissues:

Testosterone, the male sex hormone, causes increased deposition of protein in tissues throughout the body, especially the contractile proteins of the muscles (30 to 50 per cent increase). The mechanism of this effect is unknown, but it is definitely different from the effect of growth hormone, in the following way: Growth hormone causes tissues to continue growing almost indefinitely, whereas testosterone causes the muscles and, to a much lesser extent, some other protein tissues to enlarge for only several months. Once the muscles and other protein tissues have reached a maximum, despite continued administration of testosterone, further protein deposition ceases. Estrogen, the principal female sex hormone, also causes some deposition of protein, but its effect is relatively insignificant in comparison with that of testosterone **(Guyton and Hall (B), 2006)**.

5-Thyroid hormone:

Thyroxine increases the rate of metabolism of all cells and, as a result, indirectly affects protein metabolism. If insufficient carbohydrates and fats are available for energy, thyroxine causes rapid degradation of proteins and uses them for energy. Conversely, if adequate quantities of carbohydrates and fats are available and excess amino acids are also available in the extracellular fluid, thyroxine can actually increase the rate of protein synthesis. In growing animals or human beings, deficiency of thyroxine causes growth to be greatly inhibited because of lack of protein