TIGHT VERSUS CONVENTIONAL GLYCEMIC CONTROL IN CRITICALLY ILL PATIENTS

An Essay

Submitted for partial fulfillment of
Master degree in **Intensive Care Medicine**

Submitted By

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2012

INTRODUCTION

Diabetes increases the risk for disorders that predispose individuals to hospitalization; including coronary artery, cerebrovascular and peripheral vascular diseases, nephropathy, infection, and lower-extremity amputations ***(Stephen et al., 2004).***

Hyperglycemia is common in acutely ill patients, including those treated in intensive care units (ICUs).The occurrence of hyperglycemia, in particular severe hyperglycemia, is associated with increased morbidity and mortality in a variety of groups of patients ***(Simon et al., 2009).***

Hyperglycemia, be it secondary to diabetes, impaired glucose tolerance, impaired fasting glucose, or stress-induced is common in the critically ill patients.

Hyperglycemia and glucose variability in intensive care unit (ICU) patients has some experts calling for routine administration of intensive insulin therapy to normalize glucose levels in hyperglycemic patients. Others, however, have raised concerns over the optimal glucose level, the accuracy of measurements, the resources required to attain tight glycemic control (TGC), and the impact of TGC across the heterogeneous ICU population in patients with diabetes, previously undiagnosed diabetes or stress-induced hyperglycemia.

Increased variability in glucose levels during critical illness and the therapeutic intervention have recently been reported to have a deleterious impact on survival, particularly in non diabetic hyperglycemic patients.

The incidence of hypoglycemia (<40 mg/dL or 2.2 mmol) associated with tight glycemic control is reported to be as high as 18.7%, by ***Van den Berghe (2001)*** in a medical ICU, although application of various approaches and computer algorithms may improve this. The impact of hypoglycemia, particularly in patients with septic shock and those with neurologic compromise, warrants further evaluation ***(Brenda et al., 2009).***

Since the introduction of intensive insulin therapy (IIT) in the intensive care unit (ICU)-world by Van den Berghe in 2001, the concept of lowering morbidity and mortality by this intervention is a subject of a vivid discussion. Paramount effort has been put in numerous studies trying to corroborate the concept and to highlight probable mechanisms ***(Heuvel and Ellger, 2008).***

AIM OF THE WORK

This study is designed to discuss the safe management of diabetic patients as regards the pathophysiology of diabetes mellitus as a disease, pharmacology of insulin and the role of glycemic control in critically ill patients in intensive care unit.

Chapter 1

PATHOPHYSIOLOGY OF DIABETES MELLITUS

A. Glucose Homeostasis

B. Diabetes mellitus

C. Complications of diabetes mellitus

A. Glucose homeostasis

Glucose is an obligate metabolic fuel for the brain under physiologic conditions. In contrast, other organs oxidize fatty acids as well as glucose. Because of this unique dependence on glucose and because it cannot synthesize glucose or store more than a few minutes' supply as glycogen, the brain requires a continuous supply of glucose from the circulation. Facilitated diffusion of glucose from the blood to the brain is a direct function of the arterial plasma glucose concentration. At normal plasma glucose concentrations, the rate of blood-to-brain glucose transport exceeds the rate of brain glucose metabolism. However, as the plasma glucose concentration falls below the physiologic range, blood-to-brain glucose transport becomes limited to brain energy metabolism and, thus, to survival. Given the immediate survival value of maintenance of the plasma glucose concentration, it is not surprising that physiologic mechanisms

that prevent or rapidly correct hypoglycemia have evolved. Indeed, these mechanisms are so effective that hypoglycemia is an uncommon clinical event except in people who use drugs that lower glucose levels (e.g., insulin, sulfonylureas, or alcohol) ***(Cryer, 2008).***

Origins and Fates of Glucose*:*

Glucose is derived from three sources: ***intestinal absorption*** that follows digestion of dietary carbohydrates; ***glycogenolysis***, the breakdown of glycogen, which is the polymerized storage form of glucose; and ***gluconeogenesis***, the formation of glucose from precursors including lactate (and pyruvate), amino acids (especially alanine and glutamine), and, to a lesser extent, glycerol.

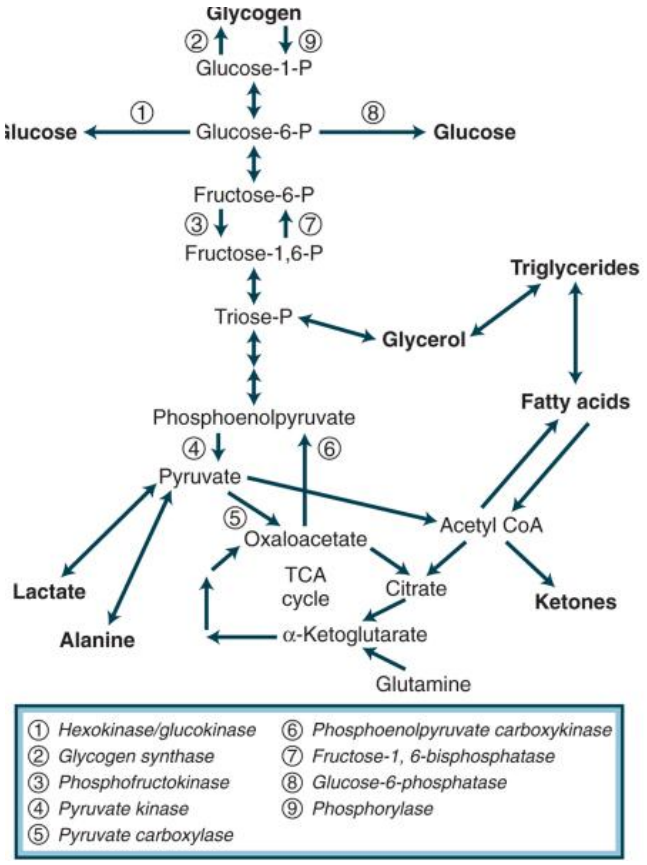

Figure (1): Glucose metabolism ***(Cryer, 2008).***

Although most tissues express the enzyme systems required to synthesize (glycogen synthase) and hydrolyze (phosphorylase) glycogen, only the liver and kidneys express glucose-6-phosphatase, the enzyme necessary for the release of glucose into the circulation, at levels sufficient to permit these organs to contribute to the systemic glucose pool. The liver and kidneys also express the enzymes necessary for gluconeogenesis (including the critical gluconeogenic enzymes pyruvate carboxylase, phosphoenolpyruvate carboxy-kinase, and fructose-1,6-bisphosphatase).

There are multiple potential metabolic fates for glucose that is transported into cells; external losses are normally negligible. Glucose may be stored as glycogen, or it can undergo glycolysis to pyruvate, which can be reduced to lactate, transaminated to form alanine, or converted to acetyl coenzyme A (CoA), which in turn can be oxidized to carbon dioxide and water through the tricarboxylic acid cycle, converted to fatty acids (and stored as triglycerides), or used for ketone body (acetoacetate, β-hydroxybutyrate) or cholesterol synthesis. Finally, glucose may be released into the circulation. As summarized in the following paragraphs, these outcomes differ in different organs ***(Cryer, 2008).***

Hepatic and Renal Glucose Metabolism:

The liver is the major metabolic regulatory organ. About 90% of all circulating glucose not derived directly from the diet comes from the liver. The liver contains significant amounts of stored glycogen available for rapid release into circulation, and is capable of synthesizing large quantities of glucose from substrates such as lactate, amino acids, and glycerol released by other tissues. In addition to controlling plasma glucose, the liver is responsible for synthesis and release of the lipoproteins that adipose and other tissues use as the source of cholesterol and free fatty acids. During prolonged starvation, the liver is the source of both glucose and the ketone bodies required by the brain

to replace glucose. The liver uses glycolysis primarily as a source of biosynthetic intermediates, with amino acid and fatty acid breakdown providing the majority of its fuel ***(Roden and Bernroider, 2003).***

The kidney has the ability to release glucose into the blood. Under normal conditions gluconeogenesis in the kidney provides only a small contribution to the total circulating glucose; however, during prolonged starvation, the kidney contribution may approach that of the liver. Kidney function is critical for glucose homeostasis for another reason; plasma glucose continuously passes through the kidney and must be efficiently reabsorbed to prevent losses ***(Roden and Bernroider, 2003).***

Glucose Utilization*:*

Muscle can store glucose as glycogen or can metabolize glucose through glycolysis to pyruvate. The pyruvate is reduced to lactate or is transaminated to form alanine or is oxidized. Lactate (and pyruvate) released from muscle is transported to the liver, where it serves as a gluconeogenic precursor (the Cori or glucose-lactate cycle). However, to the extent that lactate and pyruvate carbons are derived from glucose, they cannot result in net new glucose formation. Alanine, glutamine, and other amino acids can also flow from muscle to liver, where they serve as gluconeogenic precursors. Circulating alanine is also

largely derived from glucose (glucose-alanine cycle). Glutamine is also a major precursor for new glucose formation, although it is also partially derived from glucose (glucose-glutamine cycle). During fast, muscle can reduce its glucose uptake virtually to zero, oxidize fatty acids for its energy needs, and through proteolysis, mobilize amino acids for transport to the liver to serve as gluconeogenic precursors for net glucose formation ***(Cryer, 2008).***

Although quantitatively less important than muscle, adipose tissue can also use glucose for fatty acid synthesis or formation of glycerol-3-phosphate, which can then esterify fatty acids (derived largely from circulating VLDL) to form triglycerides. During a fast, adipocytes decrease their glucose utilization and satisfy energy needs from the beta oxidation of fatty acids. Other tissues, such as the formed elements of the blood and the renal medullae, do not have the capacity to decrease glucose utilization during fasting and therefore produce lactate at relatively fixed rates.

Glucose is the predominant metabolic fuel used by the brain under most conditions. Glucose undergoes terminal oxidation to carbon dioxide and water in the brain. The brain respiratory quotient is approximately 1.0. Although the adult brain constitutes only about 2.5% of body weight, its oxidative metabolism accounts for approximately 25% of the basal metabolic rate under

physiologic conditions. However, when ketones are plentiful in the circulation, as during prolonged fasting, they can support the majority of the energy needs of the brain and thus reduce its glucose utilization ***(Cryer, 2008).***

Systemic Glucose Balance:

Normally, rates of endogenous glucose influx into the circulation and those of glucose efflux out of the circulation into tissues other than the brain are coordinately regulated—largely by the plasma glucose–lowering (regulatory) hormone insulin and the plasma glucose–raising (counterregulatory) hormones glucagon and epinephrine—such that systemic glucose balance is maintained, hypoglycemia (as well as hyperglycemia) is prevented, and a continuous supply of glucose to the brain is ensured. This is accomplished despite wide variations in exogenous glucose influx (e.g., after feeding versus during fasting) and in glucose efflux (e.g., during exercise versus during rest) ***(Cryer, 2008).***

Table (1): Systemic glucose balance

Glucose influx into the circulation	Glucose efflux out of the circulation
Exogenous glucose delivery	Ongoing brain glucose utilization
Endogenous glucose production	Variable glucose utilization by other tissues(e.g., muscle, fat, liver, kidneys etc.) ↑ by insulin ↓ by epinephrine
In liver: glycogenolysis and gluconeogenesis ↓ by insulin ↑ by glucagon ↑ by epinephrine	
In kidneys: gluconeogenesis ↓ by insulin ↑ by epinephrine	

(Cryer, 2008)

Regulation of glucose concentration in fed state:

After an overnight fast (8-10 hours) rates of glucose production and utilization average about 2mg/dl/min. At this time the majority of the glucose is released from the liver with a small amount being produced by kidney. Carbohydrate ingestion increases glucose concentration which stimulates secretion of insulin from pancreatic β cells and suppresses secretion of glucagon from α cells. The resultant rise in insulin to glucagon ratio increases hepatic glycogen synthesis and inhibit both glycogenolysis and gluconeogenesis thereby resulting in a decrease in hepatic glucose release and an increase in hepatic glycogen content. Glucose concentration continues to rise until the rate of glucose uptake by peripheral tissues exceeds the net amount of glucose (meal-derived and endogenously produced) released from the splanchinc bed ***(Breckenridge et al., 2007).***

Glucose concentration then begins to fall toward pre-prandial levels resulting in a progressive fall in insulin and a progressive rise in glucagons concentration, which in turn permits a gradual increase in endogenous glucose production and a gradual fall in glucose utilization to basal rates.

Depending on the amount and type of food ingested, both glucose concentration and turnover are generally back to basal levels sometimes between 4 and 6 hours after the

start of a meal. Thus, the rate of carbohydrate absorption, the timing as well as the amount of insulin and glucagon secreted, the ability of the liver to store and subsequently release glucose, as well as the response of the liver, muscle, and fat to insulin and counter insulin hormones all interact to minimize the rise in glucose concentration after a meal as well as to ensure a smooth return of glucose concentration to pre-prandial levels during the transition from the fed to the post absorptive sate ***(Breckenridge et al., 2007).***

Regulation of glucose concentration in the fasting state:

The contribution of gluconeogenesis becomes progressively more important as the duration of fast is extended and hepatic glycogen stores are depleted. The rate of glycogen depletion depends on a variety of factors including antecedent diet and exercise, but is nearly complete after 24 to 48 hours of fasting. Anything that lowers the demand for glucose lessens the need to break down protein stores. This is accomplished by changing from a primarily carbohydrate-based metabolism in the fed state to a primarily fat-based metabolism in the fasted state ***(Childs, 2002).***

Insulin decreases while glucagon, growth hormone, and cortisol concentrations all increase as hepatic glycogen is depleted and the glucose concentration falls. This change in the hormonal profile stimulates lipolysis and

ketogenesis, which results in an increase in plasma glycerol, free fatty acid and ketone body concentrations. Glycerol serves as a gluconeogenic substrate, thereby sparing amino acid. Free fatty acids are metabolized by muscle, liver and other tissues instead of glucose and are converted by means of ketogenesis to acetoacetate and β-hydroxybutyrate which can substitute for glucose as a fuel for the brain. This metabolic adaptation n ormally permits glucose to gradually decrease to 40 to 50 mg/dl during a fast without provoking symptoms of hypoglycaemia ***(Childs, 2002).***

Inadequate glycogen stores or breakdown, insufficient gluconeogensis due to defects in enzyme activity, lack of substrate availability, or persistent elevations of insulin or insulin-like activity alone or in combination can cause or exacerbate hypoglycaemia ***(Childs, 2002).***

Regulation of glucose concentration during exercise:

Exercise increases glucose utilization (by muscle) to rates that can be several times greater than those of the postabsorptive state. Endogenous glucose production normally accelerates to match use so that the plasma glucose concentration is maintained ***(Childs, 2002)***.

Glucoregulatory Factors*:*

1. Hormonal Glucoregulatory Factors:

Hormones are the most important glucoregulatory factors, and the regulation of their secretion is complex. Glucose, specifically the plasma glucose concentration, is the most important determinant of the secretion of glucoregulatory hormones, including insulin, glucagon, epinephrine, growth hormone, and cortisol.

Insulin:

The dominant glucose-lowering hormone, suppresses endogenous glucose production and stimulates glucose utilization by insulin-sensitive tissues, thereby lowering the plasma glucose concentration. Insulin is secreted from beta cells of the pancreatic islets into the hepatic portal circulation and acts on the liver and peripheral tissues. It inhibits hepatic glycogenolysis and gluconeogenesis and, in concert with other factors, converts the liver into an organ of net glucose uptake and fuel storage (glycogen and triglycerides). It also suppresses renal glucose production and stimulates glucose uptake, storage, and utilization by tissues such as muscle and fat. In the postabsorptive state, insulin regulates the plasma glucose concentration primarily by restraining hepatic glucose production. Higher levels, such as those that occur after meals, are required to stimulate glucose utilization. In addition to direct actions on hepatocytes, insulin reduces hepatic glucose production