Glycemic Control In Critical Ill Patients; Literature Review Of Glycemic Targets

Thesis Report

Submitted by

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DEDICATION

This work is dedicated to my parents, who are a known type 2 diabetic.

My loveable kids Salah, Abdo, Maram and Rahaf

ABSTRACT

Background: Hyperglycemia is common in critically ill patients. Patients with hyperglycemia could be known diabetic or non-diabetic. Definitely hyperglycemia can increase morbidity and mortality in critically ill patients. Correction of hyperglycemia may improve clinical outcomes. To date, a definite answer with regard to glucose management in general intensive care unit patients, including treatment thresholds and glucose target is undetermined.

Objective: The main objective of this review to explore the impact of hyperglycemia and it is treatment on critically ill patients and which glycemic targets are safe and effective in critically ill patients.

Methodology: The type of the research is literature review. The Cochrane Library and PubMed databases were used for search. The search was limited to English publications and studies published from 1990 until April 2014. Selected papers were assessed for methodological validity using theOxford quality scoring system. Initial keywords to be used will be: Hyperglycemia, Tight glycemic control, strict glycemic control, critically ill patients and intensive insulin therapy.

Results: Apart from Van den Bergheet al. 2001 (surgical ICU) the randomized control trials and meta-analysis included in this review showed that tight glycemic control did not significantly reduce short-term mortality compared with conventional glycemic control as well the 90 days mortality was not reduced but the death rate was increased in the patients of tight glycemic control. Hypoglycemia was directly related to tight glycemic control compared with conventional glycemic control as shown in all studies when. The Van den Bergheet al. 2001 (surgical ICU) the only study included in this review showed reduced morbidity with tight glycemic control other studies included in this review did not show significantly reduction in morbidity.

Conclusion: Reviewed randomized controlled trials and meta-analyses of randomized controlled trials have shown no survival benefit of tight glycemic control and it leads to a significantly increase rate of hypoglycemia. The reviewed evidence has shown a J-shaped relationship between average blood glucose values and mortality; maintaining glucose levels of less than 180 mg/dL(10 mmol/l) is not inferior to near-normal blood glucose levels in critically ill patients and is evidently safer. Glycemic variability is also an indispensible aspect of glucose management in the critically ill patients. Higher glycemic variability may increase the mortality.

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Chapter 1

Introduction

1.1 Background of the Study:

Diabetes mellitus is simply referred as diabetes and it is the most common metabolic and chronic disease across the world. Diabetes mellitus is a non-communicable chronic disease which results due to the increased blood glucose levels. Day by day, number of people who have been affected by diabetes is increasing significantly around the world. Krinsley (2003) mentioned that, the history of diabetes is strongly associated with the poor clinical outcome. Diabetes is one of the long-lasting diseases which cannot be cured but can be controlled and it affects the population worldwide. Diabetes is a chronic disease which needs continuing patient self-management education and medical care in order to reduce the risk of long term complications and also to prevent acute complications. Diabetes mellitus can be described by three main types such as Type 1 Diabetes Mellitus, Type 2 Diabetes Mellitus, and Gestational diabetes Mellitus.Diabetes is recognized as a worldwide epidemic disease which affects nearly about 366 million people throughout the globe. IDF (International Diabetes Federation) estimated that, number of people affected by diabetes disease may increase to nearly about 552 million by 2030. According to the estimation of International Diabetes Federation, Qatar will also be positioned as one of the top of highest rates of diabetes particularly in the MENA (Middle East and North Africa) region and the prevalence of diabetes in Qatar will be around 20 percent (International Diabetes Federation, 2011). Chan et al (2009) mentioned that, more than 60 percent of population in the world with diabetes is from Asia and this is mainly due to two nations India and China which contributes the largest people with diabetes. Several researchers' reports that, in India, nearly about half the patients with diabetes have poor glycemic control. The issues of diabetes have been steadily increasing every day. Currently more of the developing countries face uncertain future with respect to the potential burden that diabetes mellitus impose upon them. At the same time, several influences affect the prevalence of diabetes throughout the world and also identifying those factors are most essential in order to facilitate change while facing health challenges.

1.2 Problem Statement:

Diabetes management still remains a challenge for both developing and developed countries. Barriers to diabetes management include both patient related and provider related issues. Physician barriers may include constraints of facilities and time, sub-optimal knowledge of guidelines, and attitudinal issues (Puder and Keller 2003). Provider issues are also most important for the appropriate diabetes management. Providers are always tend to spend more time on acute management rather than the chronic (preventive) care, competing care demands, inadequate knowledge, and delay in clinical response due to poor control and also they are not aware of most effective interventions (Hofer 2004; Fenton et al, 2006).Nearly about one in four patients are admitted to the hospital because of diabetes and approximately 30 percent of patients with diabetes need two or more hospitalizations every year. Management of hyperglycemia and diabetes in hospitalized patients acts as the major concern for the hospitals (Umpierrez et al, 2002; Clement et al, 2004; Jiang et al, 2003).The macro and micro complications are the reasons which play main role in increasing the burden of diabetes. China and India have huge number of people with cardiovascular diseases and diabetes which causes a major threat to the public health (Pradeepa 2012). The burden of diabetes complications in developing countries can have capacity to affect the younger age group and also produces serious economic implications. The complications of diabetes pose health care burden and also intended to discourage the overall quality of life (Mohan 2013).The existing studies fail to identify in detail about the diabetes management in critical illness particularly with respect to hyperglycemia. Limited studies have focused in the diabetes management in critical illness. The awareness about the diabetes and its complications is also less among the patients. Effective management of patients with diabetes is only solution to the problem of diabetes.

1.3 Epidemiology of hyperglycemia in critical ill patients:

Hyperglycemia mainly occurs in patients with undiagnosed or known diabetes or during acute illness (which means stress hyperglycemia). Generally, stress hyperglycemia is the most common issue in the critical illness. At the same time, its prevalence is most difficult and this is due to the limited data and also stress hyperglycemia has capacity to generate high risk for the clinical outcomes (Fahy 2009). Hyperglycemia in the critically ill patient comes with the worse

outcomes. Hyperglycemia occurs after severe stress (for example injury or infection) and it results from the combination of increased hepatic gluconeogenesis, increased secretion of the catabolic hormones, and resistance to hepatic and peripheral actions of the insulin. Hyperglycemia is one of the common occurrences in the intensive care unit and it is associated with the worse outcomes in both children and adults (Kong 2007; Ulate et al, 2008). Sicree (2010) mentioned that, over the last 20 years, several studies has been describing about the epidemiology of diabetes. Now, it is recognized that, developing countries are presently facing greatest burden of diabetes. At the same time, still several public health planners and governments remain largely unaware about the future potentials for the increase in diabetes and also about its complications. There is a strong need for awareness about diabetes among the people worldwide and its prevention in order to control the diabetes. Healthcare society must take combined effort in order to reduce the burden of diabetes.Hyperglycemia is a common association of critical illness without any history of diabetes mellitus. Qaseem A. (2011) mentioned that, hyperglycemia is estimated to be seen approximately 40 percent in hospitalized patients. At first, hyperglycemia was assumed to be an adaptive stress response which is favorable to survival (Van den Berghe, 2004; Van den Berghe, 2010). Over the past two decades, understanding about hyperglycemia has improved significantly. Several studies mentioned that, hyperglycemia is generally related to increased morbidity and mortality (Krinsley, 2003; Baker 2006). Hyperglycemia is common among critically ill patients and it is caused due to various mechanisms such as insufficient insulin, nutrition, and medications. Hyperglycemia generally occurs in patients with undiagnosed or known diabetes or also during acute illness (stress hyperglycemia). Donahey (2013) stated that, stress hyperglycemia is considered as one of the common problems in the critical illness. At the same time, prevalence is most difficult to establish and this is because of limited data. Marik and (2004) and Fahy (2009) stated that, stress hyperglycemia provides high danger for the adverse clinical outcomes. Umpierrez (2002) conducted an observational study on hyperglycemia and identified that, intensive care unit patients with newly diagnosed hyperglycemia have higher mortality that is nearly about 31 percent when compared with the hyperglycemia patients with known diabetes. Approximately 75 percent of all patients, including diabetes may have blood glucose concentrations more than 110 mg/dl (6.1 mmol/l) during the time of admission and nearly about 12 percent of all patients may have blood glucose concentrations more than 200 mg/dL (11.1 mmol/l) during the time of

admission (Berghe et al, 2001). Cely et al (2004) identified that, more than 60 percent, 38 percent and 23 percent of patients have blood glucose concentrations more than 110 mg/dL , 150 mg/dL and 200 mg/dL (6.1 mmol/l, 8.3 mmol/l and 11.1 mmol/l) after admission in medical intensive care unit of the tertiary care medical center respectively. Stress hyperglycemia is generally defined as the increase in the blood glucose which means above 200 mg/dL (11.1 mmol/l) in the existence of acute illness. If the hyperglycemia is left untreated, then it has capacity to lead to critical illness such as polyneuropathy, acute kidney injury, decreased wound healing, sepsis, and respiratory failure (Vanhorebeek 2005; Farrokhi 2011; Dombrowski 2013).

1.4 Pathophysiology of Hyperglycemia In critical ill Patients:

Hansen et al (2007) has mentioned that diabetes mellitus is a generally difficult and strain related hyperglycemia happening in patients devoid of record of diabetes mellitus,which has been exposed to be related with a not so good clinical result. Effectual glycemic manage in gravely sick patients with consequences in noticeable improvements in clinical results. Stress hyperglycemia is typically defined as a recent detected hyperglycemia to be greater than 200 mg/dl (11.1 mmol/l) that resolves subsequent to decision of severe illness. According to Donahey E, (2013) Stress hyperglycemia is triggered by several endogenous and exogenous influences. Endogenous influences include counter-regulatory hormones, increased insulin resistance, decreased glucose uptake and increased cytokines. Severe body stress leads to upsurge of cortisol secondary to activation of the hypothalamic– pituitary–adrenal axis. Cortisol will stimulate gluconeogenesis which lead to elevation of blood glucose in addition to that cortisol which reduces glucose utilization. Insulin resistance encouraged more by the effects of other counter-regulatory hormones, such as glucagon, catecholamine, and growth hormone, which enhance lipolysis, proteolysis, and hepatic glucose production. All of these processes impair glucose uptake into peripheral tissues, increase circulation of free fatty acids, and stimulate gluconeogenesis and glycogenolysis. Exogenous influences, such as vasopressors, parenteral and enteral nutrition, dextrose infusion, and corticosteroids, further worsen the hyperglycemia. According to D'Orazio et al (2005) factors that affect Point of Care glucose content in blood measurements includes blood source like serum, plasma; the amount of blood on glucometer. Also peripheral hypoperfusion ,vasoconstriction, shock states, and dehydration effect capillary blood glucose measurement. Substances which are noted to impede with

measurements of glucose may include Dopamine, Levodopa, Mannitol, severe unconjugated Hyperbilirubinemia , Acetaminophen, severe hyperlipidemia, high uric acid, Maltose which is present in solutions of immunoglobulin and Icodextrin, which exist in peritoneal dialysis liquid.

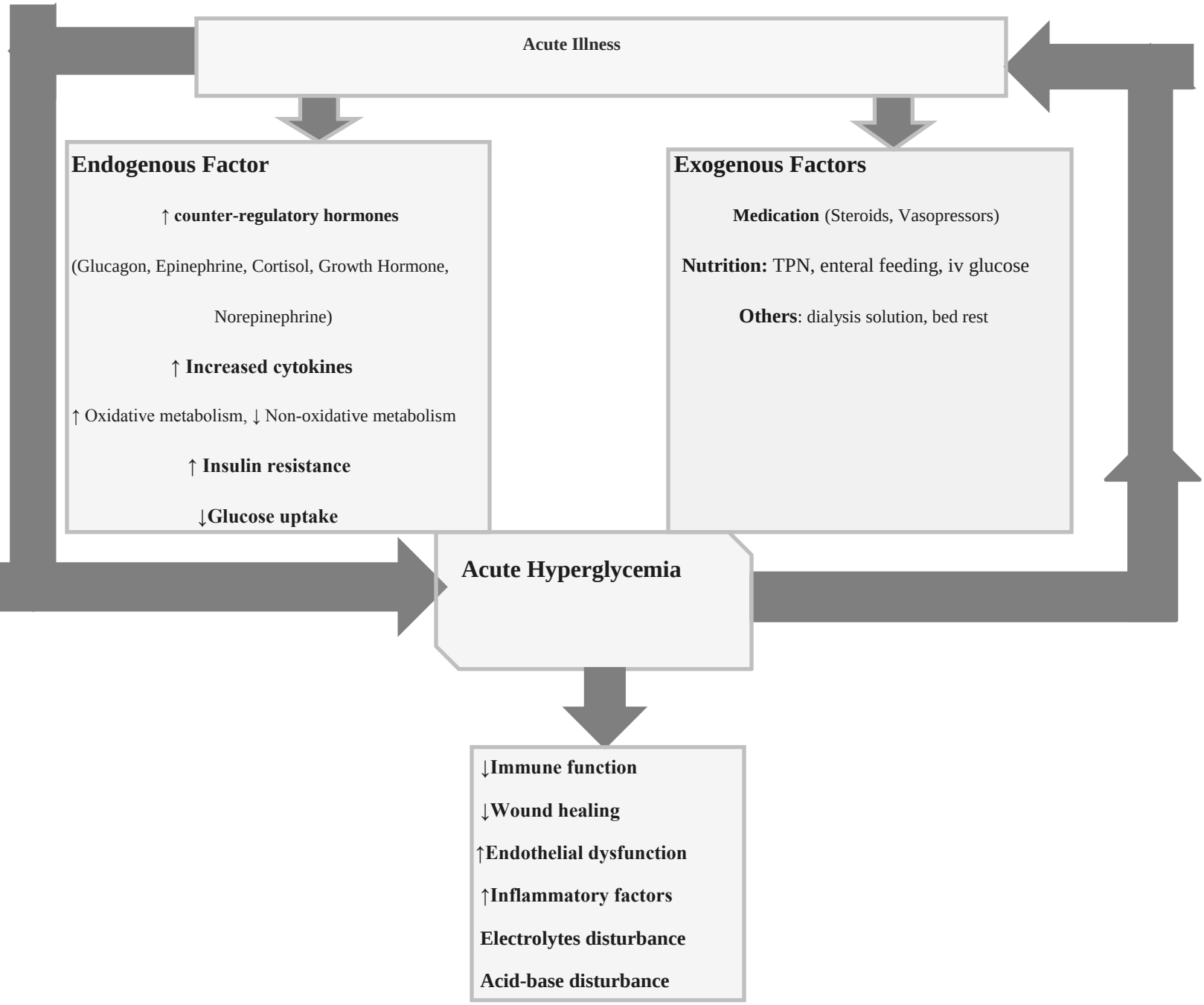

Figure (1) Pathophysiology of acute hyperglycemia modified from the study of DunganKM.

In addition to that Tumor necrosis factor-alpha may have a role by increasing plasma glucagon and gluconeogenesis (Dungan KM 2009). Acute severe illness impair the insulin signaling pathway despite increasing insulin production, causing decreased glucose transporter (Glut)-4 mediated glucose uptake, which in turn leads to insulin resistance (Cely CM 2004). The increasing in oxidative and decreasing in non-oxidative which is related to cytokine up-regulation of Glut-1 leading to increase in Noninsulin-mediated uptake. In patients with diabetes the stress related to severe illness leads to more disturbances in glucose metabolism, because the compensatory response to increase insulin secretion is deficit (Michelle A 2009).

1.5 Treatment of Hyperglycemia in Critically Ill Patient:

As recommended by ADA and AACE in critically ill patient insulin should be started for persistent hyperglycemia, at blood glucose level greater than 180 mg/dL(10 mmol/l). In the ICU setting, insulin infusion should be used to control hyperglycemia and to maintain blood glucose levels between 140 mg/dl to 180 mg/dl (7.8 to 10 mmol/l) and levels less than 110 mg/dL (less than 6.1 mmol/l) are not recommended. Validated protocols with demonstrated safety, efficacy, and low rate of hypoglycemia are recommended. With IV insulin therapy, frequent glucose monitoring is required (Moghissi, E.S. et al 2009). In critically ill patients to control the hyperglycemia a validated intravenous insulin infusion protocol that has demonstrated efficacy and safety in achieving a target glucose range without increasing the risk of severe hypoglycemia is required as recommended by the American Diabetes Association. The best insulin infusion protocol should be as :-

a) blood glucose control reached in a sound timeframe
b) minimal hypoglycemic risk
c) have a low operator error rate
d) Require minimal nursing time.

The IV insulin administration is much effective and predictable in managing hyperglycemia than subcutaneous insulin therapy. Once the condition of patient stabilizes, infusion of IV insulin can be transitioned to subcutaneous insulin therapy. It is essential that consideration must be given to medications and nutritional status of patient with continuation of glucose supervision to guide the ongoing adjustments in dose of the insulin as modifications as sensitivity of insulin can exist during acute illness. During the transition to subcutaneous insulin bolus and a basal regimen of

insulin has been described to be efficient and protective in surgical and medical patients. The basal insulin is offered as an injection of basal insulin analogs provided every 24 hours or intermediate acting human insulin given every eight to twelve hours. Prandial insulin is given with regular insulin of human or with rapid acting analogs of insulin. Regular insulin has a gradual action onset and must be injected 30 to 45 minutes before a meal. The safety and effectiveness of premixed preparations of insulin have not been verified in hospitalized patients. Additionally the use of non-insulin and oral therapies are not recommended in critically ill patients.

1.6 Justification, Aims and Objectives of the Study

Hyperglycemia in critically ill patients is not a uncommon problem in intensive care (Krinsley JS 2003). The hyperglycemia is related to increased mortality and morbidity (Marik PE 2004). Glycemic control targeting blood glucose levels of 80mg/dl to 110mg/dl (4.4 to 6.1 mmol/l) denoted to as tight glycemic control. Morbidity and mortality among critically ill patients were reduced by tight glycemic control as concluded in two randomized controlled trials (Van den Berghe G 2001, 2006). Latest meta-analysis looked for the benefit of tight glycemic control did not confirm that (Wiener RS 2008). Some studies concluded increase hypoglycemic risk in patients with tight glycemic control (Brunkhorst FM) and the other studies did not demonstrate that. Some studies recommend keeping blood glucose levels less than 150 mg/dl (8.3 mmol/l) while other studies found blood glucose levels of 180 mg/dl (10 mmol/l) is better to apple in patients with critically ill patients to adhering to the tight in terms of mortality and morbidity in contrast with tight control (Finfer S 2009). Still the controversies of how and for whom tight glycemic control is safe and effective remains quite elusive (Chase JG 2007). The objective of this literature review is to look into the depth ,and important studies has been done in this filed to try and reach conclusions answering the questions related to the impact of hyperglycemia and its treatment on critically ill patients and which glycemic target more safe to such kind of patients.

The following are the primary and secondary objectives of this research:

Primary Objectives:

The main objective of this review is to explore the impact of hyperglycemia and its treatment on critically ill patients and which glycemic targets are safe and effective in critically ill patients.

Secondary Objectives:

- To identify the adverse effect of hypoglycemia in critical ill patients
- To identify the benefits of glycemic control in the critically ill patients
- To identify the treatment modalities of hyperglycemia in critically ill patients

1.7 Research Questions:

What is the impact of hyperglycemia and it is management on critically ill patient and what is the optimal glycemic target?

Chapter 2

Methodology

The type of the research is literature review. In this research we will study the effect of glycaemic control on the critically ill patients. It has been seen that there is a debate on whether the glycaemic control could reduce the number of mortality cases among the critically ill patients. The same is being studied here thorough data collection and analysis .

2.1 Search Strategy:

The Cochrane Library and PubMed are the databases that will be used for the search. The search will be limited to English publications and studies published from 1990 until April 2014. A three- step search strategy will be used in this review. An initial limited search of databases will be undertaken followed by analysis of the text words contained in the title. A second search using all identified keywords will then be undertaken across all included databases. Thirdly, the reference list of all identified reports and articles will be searched for additional review. Selected papers before conclusion for this review will be assessed for methodological validity using theOxford quality scoring system. Initial keywords to be used will be: Tight glycemic control, strict glycemic control, critically ill patients and intensive insulin therapy.

2.2 Types of Studies included in this review:

This review will include the following type of studies:

(1) Meta-analysis
(2) Multicenter randomized control trials
(3) Single center randomized control trials

2.3 Inclusion Criteria:

This literature review will review studies that include adult patients over the age of 18 yearsthat had been admitted to intensive care units surgical, medical or mixed because of different diagnosis like severe sepsis, acute myocardial infarction, stroke or perioperative, and they received intensive insulin treatment targeting tight glycemic control or standard treatment targeting conventional control. The patients could be known diabetic regardless of past glucose control treatment modality or with stress induced hyperglycemia.

2.4 Types of Interventions:

This review will include studies that evaluate efficacy of tight glycemic control as per study definitions in comparison with conventional glycemic control, on all patients admitted to intensive care units and received glucose control treatment during their stay in intensive care unit.

2.5 Types of Outcomes:

This review will evaluate studies that include the following outcome measures:

(1) Mortality in intensive care unit
(2) Mortality during the first 4 weeks
(3) Length of stay in ICU
(4) Time on mechanical ventilation
(5) Cardiac arrhythmia
(6) Deep sternal infection
(7) Acute renal failure

2.6 Assessment of Methodological Quality:

Selected papers before conclusion for this review will be assessed for methodological validity using theOxford quality scoring system.

2.7 Data Collection:

Data will be extracted from papers included in the review using the standardized data extraction tool. The data extracted will include specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives.

2.8 Limitations of the Research:

- This study discusses only about the hyperglycemia in critical ill patients.
- This study does not include non-published studies.
- Acute complication of diabetes beyond scope of this study.

Chapter 3

Results

PubMed and Cochrane databases were used in the search. 1362 studies were identified as potentially eligible from initial literature search. After screening of study titles, 118 studies were selected for abstract review and after review of abstracts, 61 articles were considered of interest and full text was retrieved for detailed evaluation. Due to the inconsistency with the predefined inclusion criteria, 20 of the 61 articles were selected subsequently. Thus, a total of 20 eligible randomized controlled trials and meta-analysis were included in this review of literature. Detailed search steps were described in Figure(2).

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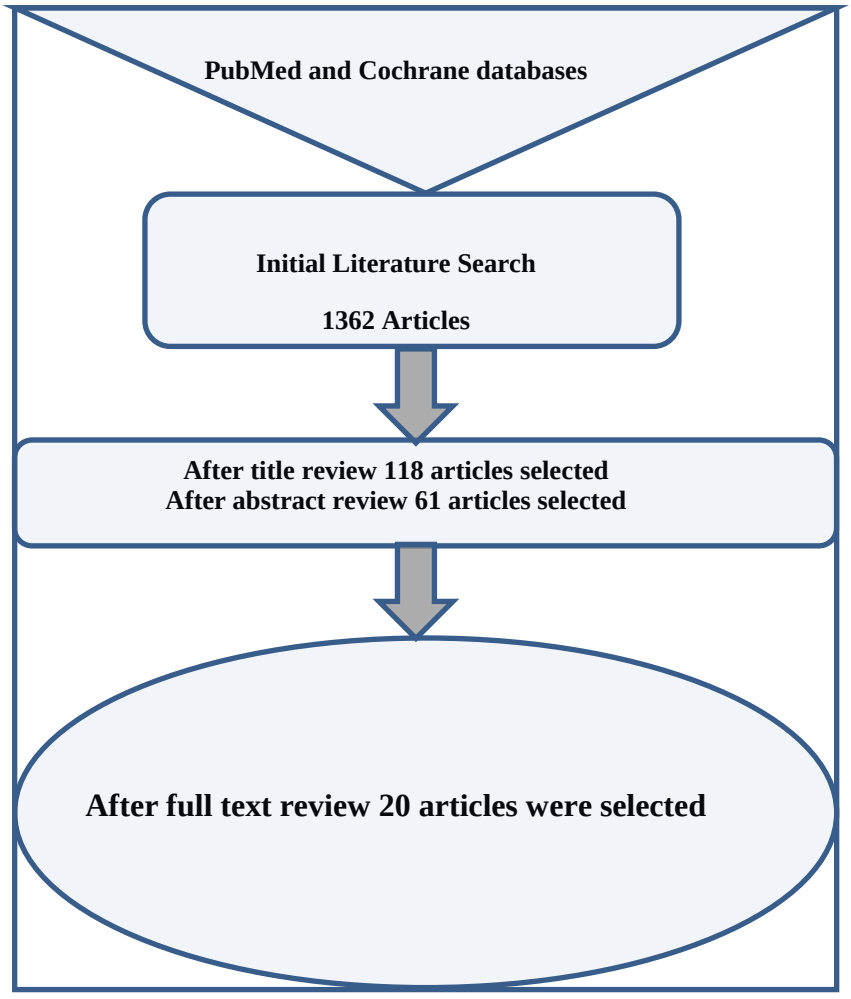

Figure(2) Flow diagram of articles search and selection

Study	Randomizd	Method to generate randomizatin sequence described and appropriate	Method to generate randomization sequence described but inappropriate	Double blind	Method of double-blinding described and appropriate	Method of double-blinding described but inappropriate	Withdrawals and dropouts described	Total Oxford score
Van den Berghe et al.(surgical ICU)	Yes	Yes	No	No	No	No	Yes	3
Van den Berghe et al.(medical ICU)	Yes	Yes	No	No	No	No	Yes	3

Table (1) Oxford quality scoring system of randomized controlled trials included in this study

Arabi et al.	Yes	Yes	No	No	No	No	Yes	3
Brunkhorst et al.	Yes	Yes	No	No	No	No	Yes	3
NICE-SUGAR Study	Yes	Yes	No	No	No	No	Yes	3
Glucontrol study	Yes	Yes	No	No	No	No	Yes	3
COIITSS study	Yes	Yes	No	No	No	No	Yes	3

In the methodological assessment of the studies included in this review , were no sign for heterogeneity and all the included studies got 3 out of 5 according to Oxford scoring system.

Apart from Van den Bergheet al. 2001 (surgical ICU) the randomized control trials and meta-analysis included in this review showed that tight glycemic controldid not significantly reduce short-term mortality compared with conventional glycemic control as well the 90 days mortality was not reduced but the death rate was increased in the patients of tight glycemic control. Hypoglycemia was directly related to tight glycemic control compared with conventional glycemic control as shown in all studies . The Van den Bergheet al. 2001 (surgical ICU) the only study included in this review showed reduced morbidity with tight glycemic control other studies included in this review did not significantly reduce morbidity.

Chapter 4

Adverse Effect of Hyperglycemia in Critical Ill Patients

Lewis et al (2004), Berghe (2004) and Berghe et al (2003) have pointed out that Hyperglycemia would support osmotic diuresis leading to hypervolemia with electrolyte abnormalities which encompassing hypomagnesaemia, hypokalemia and hypophosphatemia. Moreover, According to Oliver and Opie (1994) and Dandona, (2002) stated that hyperglycemia would affect catabolism particularly in the skeletal muscle. Other effects of hyperglycemia include an increase inflammatory cytokines, attenuated host defiance, increase coaguability, maximize oxidative stress, and endothelial dysfunction (Berghe, 2004, Lewis et al, 2004, and Mohanty, 2002). Further Zerr et al (1997) also stated that hyperglycemia increases susceptibility and affects the immune function that would result in infection. At the same time, it was also noticed that hyperglycemia would also impair platelet and fibrinolysis function that would result in hypercoagulability and maximized risk of thrombotic events (Berghe, 2004 and Dandona, Aljada and Mohanty, 2002). Addition to these, Langouche et al (2005) also pointed out that glucose causes abnormalities in endothelial dysfunction and vascular reactivity. Moreover, endothelial dysfunction would lead to the compromised microcirculation. Corresponding cellular hypoxia would result in failure of organ and increase rate of death in critically ill patients. Apart from these Brownlee (2005) discussed about the complexities in diabetics. Overload of cellular glucose and vulnerability to toxicity of glucose would occur since deficient scavenging and maximized generation of ROS (reactive oxygen species) come by oxidative phosphorylation and glycolysis. Hyperglycemia-induced overproduced mithochondrial superoxide that produces four pathways such as protein kinase C activation, polyol pathway, advanced glycation products production and maximized hexosamine pathway included in the complications of diabetic pathogenesis. Steinberg et al (2000) and Oliver (1994) pointed out that hyperglycemia is linked with maximized FFA levels (Free Fatty Acids) which would maximize myocardial oxygen needs and therefore ischemia; affect endothelial NO (nitric oxide) production and thus impair the endothelium vasodilatation; induce cardiac arrhythmias and minimize myocardial contractility. Additionally, Mesotten et al (2004) illustrated that high concentration in FFA would maximize the generation of ROS (reactive oxygen species) in mononuclear cells as well as produce insulin resistance in hepatocytes and myocytes. Excess of FFA has many consequences namely

lipotoxicity that is a crucial feature of failure in multiple organs (Steinberg et al, 2000 and Langouche et al, 2005).

Capes et al (2000), Gore et al (2001) and Williams et al (2002) had discussed about the adverse effects of hyperglycemia. They had been witnessed that hyperglycemia would result in poor clinical results and complications. According to Srinivasan et al (2004) concentrations of elevated blood glucose are linked with maximized mortality and morbidity after surgery, burns, strokes, head trauma and MIs. It was also noted that hyperglycemia could result in dysfunction of polymorphonuclear neutrophil and minimize the opsonic activity (Rassaias et al, 1999) and intracellular bactericidal which plays a key part in increasing the infections incidence in patients with hyperglycemia (Rassias et al, 1999 and Perner, 2003). Additionally, Flakoll (1993) and Berghe (2004) have stated that acute hyperglycemia increase proteolysis and are integrated with maximized risk of hemodynamic instability, cardiac complications, acute renal failure, electromycardial disturbances and death (Cheung, 2005 and Burkett, 2009).

Hyperglycemia leads to various physiologic complications. Elevations in the blood glucose have ability to cause endothelial dysfunction and mitochondrial injury, suppressing immunity and lead to the increased risk for infection (Vanhorebeek 2005; Farrokhi 2011; Dombrowski 2013). Leibowitz (2010) mentioned that, patients with stress hyperglycemia, particularly those in post-cardiothoracic surgery are generally at increased risk for wound infection. In addition to these, skin graft failure in burn patients is strongly related with the uncontrolled hyperglycemia (Gore 2001). The risk for infection is highly associated with hyperglycemia and it occurs over multiple populations. Stress hyperglycemia is strongly related with the increased risk especially for critical illness polyneuropathy. Patients with critical illness polyneuropathy were found to have longer intensive care unit stays and prolonged mechanical ventilation time. Bolton, (1996) and Schweickert (2007) stated that, hyperglycemia plays a major role in critical illness polyneuropathy as well. Glucose fluctuations may have ability to trigger adverse events that results from hyperglycemia via increased oxidative stress, apoptosis, and cytokine expression (Inzucchi, 2006). Uncontrolled hyperglycemia predisposes to adverse outcomes and at the same time glycemic control acts to be a neglected part of the patient management. Falciglia and colleagues (2009) conducted a study on critically ill patients who were affected by hyperglycemia related mortality. Authors analyzed nearly about 260,000 intensive care unit

admissions and identified that, mortality is associated with increasing blood glucose and it is independent of baseline disease severity. Krinsley (2003) stated that, moderate hyperglycemia during the intensive care unit stay has been linked with higher mortality. The significant reduction in the overall mortality was related with the blood glucose target which is less than 150 mg/dL (8.3 mmol/l) (Jacobi, 2012). In general, the risks for mortality also varies based on the patients' baseline comorbidities. Intervention trials of insulin therapy are generally limited but lowering the glucose can significantly improve the outcomes. Pomposelli et al (1998) stated that, pronounced hyperglycemia leads to the poor clinical outcome and complications. Elevated blood glucose concentrations are related with increased mortality and morbidity after head trauma, strokes, burns and surgery (Capes 2000; Gore 2001; Williams 2002).Hyperglycemia can cause decreased intracellular bactericidal, opsonic activity, and polymorphonuclear neutrophil dysfunction which plays major role in the increased occurrence of infections in critical ill patients with hyperglycemia. Apart from these, high glucose concentrations in cells can have ability to damage mitochondrial protein, modify innate immune system, exacerbate inflammatory pathways, and impair endothelial function. Nazir et al (2006) stated that, high glucose concentrations also have ability to reduce endothelial nitric oxide production and vascular reactivity which in turn compromise the blood flow to the periphery. When one looks at the patients having acute myocardial infarction, it had been seen that on admission,the blood glucose levels which were above 180 mg/dl (10 mmol/l) was related to a higher risk of cardiac failure and cardiogenic shock (Dowdy DW ,2008).Plasma glucose which was seen at the admission was also found to be an independent predictor in the long-term outcome when analysed from the non-diabetic patients who were suffering from acute myocardial infarction (Dowdy 2008).It has been noticed that in the span of 1.5-2.5 year the patients with acute myocardial infarction < 30% died, and at the same time 10% were hospitalized in case of heart failure, and 6% were admitted for nonfatal re-infarction (McCowen KC 2001).These set of patient had higher blood glucose in comparison to the patients not having such complications. It has been found in the analysis of 15 studies, that the patients who did not have diabetes and had a glucose level more than the range of 110-145 witnessed a 4 times higher risk of death in comparison to the patients who do not have diabetes and had low blood glucose levels. (Dowdy DW 2008)When one looks at the patients having acute MI, it has been seen that on

admission the blood glucose levels which were above 180 mg/dl (10 mmol/l) was related to a higher risk of cardiac failure and cardiogenic shock (Dowdy DW ,2008).

Bruno et al have shown that the worse neurological outcome in 3 months were shown in ischemic stroke patients who were admitted with a higher blood glucose level as per the multivariate logistic regression analysis done for the diabetes mellitus, stroke severity, and other vascular risk factors studies in the research (McCowen KC 2001). Also a study on the In-Hospital patients showed that hyperglycemia is not just an independent marker in the in-hospital mortality in intensive care unit but will also be seen in the patients of the general hospital wards. In the given research the investigators have segregated the patients in 3 groups that is, those who have a history of diabetes, patients with new hyperglycemia and the third were the ones with normoglycemia (Dowdy DW 2008). It was seen that the Total mortality was seen to be higher in the patients who had new hyperglycemia which stood at 16 percent in comparison to the diabetic patients which stood at 3 percent and normoglycemic patients which stood at 1.7 percent (McCowen KC 2001)

Thus it can be summarized that hyperglycemia is linked with maximized mortality and morbidity. Hyperglycemia is associated with increased incidence of infection, acute renal failure as well as the increased number of days in intensive care and time of mechanical ventilation. In addition to it hyperglycemia will worsen the prognosis of patients with stroke, burns and severe sepsis. Hyperglycemia plays a major role in critical illness polyneuropathy as well.

Chapter 5

Benefits of Glycemic Control in Critical Ill Patients

Hyperglycemia is common in critically ill patients with and without diabetes. Hyperglycemia, was considered to be a proper response to stress, is currently being recognized as a predictor of adverse outcomes including mortality and morbidity (Clement, S 2004). Hyperglycemia is common in critically ill adult patients, and it is associated with increased morbidity, such as increased length of stay in the intensive care unit, amplified risk of infections (Wisam, K 2004). Evidently in critically ill adult patient controlling of hyperglycemia associated with drop of mortality and morbidity rate as shown by clinical evidence. Numerous studies have recognized the benefits of hyperglycemia control in critically ill adult patients.

Malmberg, et al (1997) did a multi-center double-blinded, prospective randomized study the Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI). In this study the investigators looked for long-term all-cause of mortality. The study was done in nineteen coronary care units in Sweden. 620 patients were enrolled in the study. The patients who enrolled in the study were known diabetic, newly diagnosed type 2 diabetes or with stress hyperglycemia. The investigators randomly distributed patients to two groups. The first is insulin treatment group, treated with insulin infusion for at least 24 hours targeting blood glucose levels of 126 to 180 mg/dl (7 to 10 mmol/l). The second group is the control group which only receives insulin treatment as needed. The two groups received the usually management of their acute myocardial infarction. All patients were followed up prospectively for one year; and then the patients were followed up by their physician and the mean follow up period was 3.4 years. The DIGAMI Trial showed a 30 percent reduction in mortality at 1 year in the insulin treatment group (18.6 percent vs. 26.1 percent $p<0.027$). The reduction in death rate was maintained at the mean follow up period of 3.4 years, with 33 percent in the insulin treatment group versus 44 percent in the control treatment group ($p=0.011$) (Davies, M J 2002). The total reduction in risk of death was 11 percent which likens to one life saved for every nine patients treated via the DIGAMI protocol (Davies, M J 2002).

The incidence of postoperative wound infections (sternal wound infection) in diabetic patients was reduced by maintains mean blood glucose levels below 200 mg/dl (11.1 mmol/l) in the immediate postoperative period this was demonstrated through an observational study in which

the data was collected prospectively for 2467 post-operative patients (Furnary AP 1999). Furnary AP and his group compared intensive insulin protocol of intra-venous insulin every 1–2h targeting blood glucose of 150 to 200 mg/dl (8.3 to 11.1 mmol/l) with control group treated with subcutaneous insulin every 4 h targeting blood glucose levels at or below 200 mg/dl (11.1 mmol/l). They concluded a significant reduction in the incidence of deep sternal wound infections in patients received intra-venous insulin compared with the subcutaneous group (2.5 percent versus 5.3 percent, $p < .0001$) (Furnary AP 1999).

Van den Berghe G and colleagues in 2001 conducted a single center trial of 1548 patients from surgical intensive care unit (the Leuven surgical trial). They looked for the difference in mortality and morbidity in surgical critically ill patient who received intravenous insulin targeting blood glucose levels of 80 to 110 mg/dl (4.4 to 6.1 mmol/l) and surgical critically ill patient who received intravenous insulin only when blood glucose levels exceed 215 mg/dl (11.9 mmol/l) targeting blood glucose levels of 180 to 200 mg/dl (10 to 11.1 mmol/l). Intravenous glucose 200 to 300 grams was given to all patients involved in this trial during the first day of intensive care unit admission (van den Berghe G 2001). Parenteral nutrition was added to the patient enteral nutrition in second day of intensive care unit admission if necessary to achieve the caloric goal. The mean age in this study was 63 years and 71 percent were male. 63 percent of the patients had cardiac surgery. Most of the patients were not severely ill and the mean APACHE II score (Acute Physiologic and Chronic Health Evaluation II score) was 9. The study had shown that: in patients who received intensive insulin therapy the mean blood glucose was significantly lowers (103 versus 153 mg/dl {5.7 versus 8.5 mmol/l}). The mortality in intensive care unit in patients who assigned to intensive insulin therapy was significantly less (4.6 versus 8 percent) and patients on intensive insulin therapy who stayed 5 days or more in intensive care unit benefit more than others. Tight glycemic control by using intensive insulin therapy significantly reduced the hospital mortality (7.2 versus 10.9 percent). Investigators also found that the morbidity was reduced in patients received intensive insulin therapy; critical illness polymyoneuropathy, acute renal failure, transfusion requirement, and blood stream infections all were less in patients who received intensive insulin therapy. Blood glucose of less than 40 mg/dl (2.2 mmol/l) which define the hypoglycemia was more frequent in patients received intensive insulin therapy (5.1 versus 0.8 percent). Van den Berghe G and colleagues also found that the mortality rate was high in control group and this was mean concern in this study, the intensive

care unit mortality in control group was 8 percent and hospital mortality was 11 percent this mortality rate higher than mortality rate recorded for most patients undergoing routine cardiac surgery (van den Berghe G 2001).

In 2002 Finney, et al., and his group studied prospectively whether blood glucose level or quantity of insulin administration is associated with reduced mortality in critically ill patients. 531 patients newly admitted to medical and surgical intensive care unit in single center were enrolled in this trial. The primary endpoint was intensive care unit death rate. Secondary endpoints were hospital death rate, intensive care unit and hospital length of stay, and predicted threshold glucose level associated with risk of death (Finney, et al. 2002). The investigators allotted the patients to six bands of glycemic control were prospectively demarcated and each band well-defined a range of blood glucose values. Each patient had fall into some bands from admission till discharge and the extent of time each patient spent within each of the six bands was calculated (Finney, et al. 2002). The target blood glucose level was a range between 90 to 145 mg/dl (5 to 8 mmol/l) using a continuous insulin infusion. They concluded that mortality increased with increased insulin administration (OR>1), indicating that glucose control rather than administration of exogenous insulin was the leading factor in improving mortality. The outcomes of this study proposed that patients who spent less time in higher glucose bands were less likely to die than those who spent the most time in higher glucose bands (Finney, et al. 2002).

Krinsley, J S in 2002 did study included 1600 patients were admitted to mixed medical and surgical intensive care unit. He registered 800 patients retrospectively before glycemic management protocol started in his institution and another 800 patients were registered after glycemic management protocol started in his institution. Krinsley investigated the effect of the protocol on glycemic control and the effect of protocol on morbidity; transfusion requirements, bloodstream infections acquired in the intensive care unit, new renal dysfunction after intensive care unit admission, and length of stay in the intensive care unit and hospital mortality (Krinsley, J S 2004). The insulin infusion protocol started if blood glucose exceeds 200 mg/dl (11.1 mmol/l) in two successive occasions targeting blood glucose level of less than 140 mg/dl (7.8 mmol/l) and subcutaneous regular insulin is used for lower blood glucose levels (Krinsley, J S 2004). He found that blood glucose levels improved significantly with use of glycemic management protocol. 29.3 percent was the hospital mortality during the protocol period, with

Table (2) Summaries of the studies included in Benefits of Glycemic Control in Critical Illness

Authors	Type of Studies	Number of Patients	Type of Patient	Intervention	Study End Point	Result
Davies, M J 2002	RCT	620	AMI	Insulin treatment to keep BS 126 to 180mg/dl of minimum 3 months VS CT	Mortality	Significant reduction in mortality in patients treated with insulin
Furnary AP 1999	POS	2,467	Post-operative	CII to keep BS 150 to 200mg/dl VS SCI to keep BS at or < 200 mg/dl	Incidence of deep sternal wound infection	Significant reduction in the incidence of deep sternal wound infections in patients received CII
van den Berghe G 2001	RCT	1548	Surgical	TGC VS CGC	Mortality	Significant reduction in mortality and morbidity in patients treated with TGC
Finney, et al. 2002	POS	531	Medical and surgical	Insulin quantity administrated VS BS control	Mortality	Mortality increased with increased insulin administration
Krinsley, J S 2004	ROS	800	Medical and surgical	GMP VS Standard Management	Mortality	Significant reduction in mortality and morbidity in patients treated with GMP
Gabbanelli, et al. 2005).	ROS	412	Medical and surgical		Mortality	Increased mortality in patients with BS > 141.7 mg/dl
Leibowitz G 2010).	POS	410	Surgical	TGC VS CGC	Clinical outcomes	Improved clinical outcomes

RCT = Randomized Control Trail, TGC = Tight Glycemic Control, CGC = Conventional Glycemic Control, BS = Blood Sugar, GMP = Glycemic Management Protocol, POS=Prospective, Observational Study, ROS=Retrospectively Observational Study

118 patients (14.8 percent) in the treatment group versus 167 patients (20.9 percent) in the control group (p=0.002). Mean length of stay in the intensive care unit decreased from 3.58 days

in the control group to 3.19 days in the treatment group (p=0.11). There was no significant difference in the number of patients with bloodstream infections between the two groups (27 patients in the baseline group versus 21 patients in the treatment group). The protocol resulted in significantly improved glycemic control and was associated with decreased mortality and length of stay in the intensive care unit in a various population of critically ill adult patients (Krinsley, J S 2004).

Gabbanelli, et al., in his a retrospective clinical study involving 412 patients admitted to the intensive care unit found that higher intensive care unit mortality in patients whom the mean blood glucose levels were greater than 141.7 mg/dL (7.9 mmol/l), the probability of death was higher than in the group of patients in whom a strict blood glucose control was maintained (Gabbanelli, et al. 2005).

In post-operative period in patient with vascular surgery intensive glucose control was related with reduction in the all-cause death, myocardial infarction, and acute heart failure (Subramaniam B 2009). in patients undergoing heart surgery maintaining blood glucose level between110 to 150mg/dl (6.1 to 8.3 mmol/l) throughout the hospital stay, was associated with a 6 percent reduction in infection rates and a 12 percent reduction in atrial fibrillation, with differences no between-group in mortality (Leibowitz G 2010).

In summary critically ill patients are at increased risk of hyperglycemia and it is sequences. Hyperglycemia can cause many adverse outcomes in critically ill patients, including increased risk of infections, increased length of stay in intensive care unit and increased mortality. Treatment of hyperglycemia as shown in clinical trials associated with reduction in mortality and morbidity.

Chapter 6

Glycemic Target in Critical Ill Patients

Critically ill adult patients who are known to have diabetes or not known to have diabetes may be exposed to the risk of hyperglycemia. Improvement of glycemic control is linked to lower the rate of hospital mortality as shown in randomized and observational controlled studies. Intravenous insulin infusion is the most safe and preferred regimen for critically ill adult patients with hyperglycemia to achieve the glycemic control. Subcutaneous insulin therapy in calculated nutritional fixed doses and correction doses is the best option to achieve and maintain control of the blood glucose when the critically ill adult patients passed the critical stage (Farrokhi, Smiley and Umpierrez, 2011).

The safe and finest target of blood glucose in critically ill adult patients is still controversial and because of clear evident hyperglycemia, related adverse effects all clinical experts wanted to treat and prevent hyperglycemia. Many clinical trials were conducted to examine and find out the optimal glycemic target in critically ill patients.

Wiener RS and colleagues (2008) conducted a meta-analysis of 29 studies of randomized controlled trials including 8432 patients using intensive insulin therapy targeting blood glucoslevels of less than 150 mg/dl (less than 8.3 mmol/l) compared with usual care and usual care different from study to study in term of treatments and targets. Wiener RS and colleagues concluded that hospital mortality in critically ill patients was not significantly reduced by tight glycemic control of blood glucose and hypoglycemic risk was significantly increased. Mortality endpoint data was presented on 27 studies, in which 16 of 27 studies tight glycemic control was preferred and in 11 of 27 studies the usual care was preferred. Statistically significant relative risk reductions were in only 2 of the 16 studies that preferred tight glycemic control (at a 95 percent confidence interval) and none of the 11 studies that preferred usual care. Reduced risk for septicemia which was limited to surgical intensive care patients and not medical intensive care unit patients was the only positive outcome from tight glycemic control (Wiener RS 2008). Griesdale DE and his group (2009) carried out a meta-analysis of 26 trials including 13,567 patients compared tight glycemic control of blood glucose of 150 mg/dl or less (8.3 mmol/l or less) with usual control. No substantial reduction in mortality and six-fold increase in the risk of

hypoglycemia between critically ill patients with tight glycemic control were the conclusion of Griesdale DE and his group. Griesdale DE and his group stated that patients in surgical intensive care unit might benefit from tight glycemic control with a resulting mortality risk ratio of 0.63 (95 percent confidence interval 0.44–0.91) but this was not shown in patients admitted to medical or mixed intensive care units (Griesdale DE 2009).

Marik PE and his colleagues did another meta-analysis of 7 randomized controlled trials including 11,425 patients were admitted to surgical or medical intensive care unit. They were comparing tight glycemic control of blood glucose levels 80 to 110 mg/dl (4.4 to 6.1 mmol/l) with conventional control. They concluded, intensive insulin therapy did not show reduction in 28 days mortality as well as there was no reduction in incidence of need for renal replacement therapy and sepsis. Risk of hypoglycemia in this study was significantly higher in critical ill patients with tight glycemic control. The investigators noted important relationship between the amount of parenteral calories delivered to the patients and mortality (Marik PE 2010).

Friedrich JO and his colleagues (2010) did a meta-analysis of 26 trials including 13,567 critically ill patients admitted to medical or surgical intensive care units comparing tight glycemic control of blood glucose of less than 150 mg/dl (less than 8.3 mmol/l) with conventional control of blood glucose. The investigators in this study distributed the patients to two groups, group one patients with medical diagnosis and group two patients with surgical diagnosis. Friedrich JO and his colleagues established that the intensive insulin therapy targeting blood glucose levels of less than 150 mg/dl (less than 8.3 mmol/l) did not reduce mortality in both group of patients with surgical or medical diagnosis (Friedrich JO 2010).

Kansagara D and his colleagues in 2011 did a meta-analysis of 21 randomized controlled trials including 14,768 patients, from intensive care units, peri-operative care, myocardial infarction, cerebrovascular accident, and traumatic brain injury. Intensive insulin therapy targeting tight glycemic control of blood glucose levels less than 120 mg/dl (6.6 mmol/l) was compared with conventional control in this study, and the conclusion was, no evidence of improving short term mortality in group with tight glycemic control in all hospital locations and more clear in intensive care patients. Hypoglycemic risk was significantly increased in patient with tight glycemic control. (Kansagara D 2011)

A meta-analysis of five randomized trials included 1972 from surgical intensive care unit compared intensive insulin therapy to less stringent glycemic control. Intensive insulin therapy

targeted blood glucose levels of less than 150 mg/dl (less than 8.3 mmol/l). Significant lower level of mortality was demonstrated in patients with intensive insulin therapy (7.4 versus 11.8 percent, relative risk 0.63, 95% CI 0.44-0.91) (Griesdale DE 2009).

Table (3) Characteristics of Meta-analysis included in this review

Authors	Number of Studies	Type of Studies	Number of Patients	Type of Patient	Intervention	Study End Point	Result
Wiener RS 2008	29	RCT	8432	Mix surgical and medical	Compare TGC VS CGC	Mortality	No difference in mortality, increased risk of hypoglycemia, Decreased risk of septicemia in surgical patients with TGC.
Griesdale DE 2009	26	RCT	13,675	Mix surgical and medical	Compare TGC VS CGC	Mortality	No difference in mortality, 6 folds increased risk of hypoglycemia in patients with TGC.
Marik PE 2010	7	RCT	11,425	Mix surgical and medical	Compare TGC VS CGC	28 days Mortality	No difference in 28 days mortality, increased risk of hypoglycemia in patients with TGC.
Friedrich JO 2010	26	RCT	13,567	Mix surgical and medical	Compare TGC VS CGC	Mortality	No difference in mortality, increased risk of hypoglycemia in patients with TG

Authors	Number of Studies	Type of Studies	Number of Patients	Type of Patient	Intervention	Study End Point	Result
Kansagara D 2011	27	RCT	14,768	Mix surgical and medical	Compare TGC VS CGC	Mortality	No difference in mortality, increased risk of hypoglycemia in patients with TG
Griesdale DE 2009	5	RCT	1972	surgical	Compare TGC VS CGC	Mortality	Significant lower level of mortality was demonstrated in patients with intensive insulin therapy

RCT = Randomized control trial, TG = Tight Glycemic Control and CG = Conventional Glycemic Control.

The European Glucontrol study which is large multicenter randomized controlled trial from 21 intensive care units throughout Europe recruited 1101 patients. During the study both medical and surgical intensive care unit patients were randomly allocated to two groups one group with intensive insulin treatment targeting blood glucose levels of 80 to 120 mg/dl (4.4 to 6.6 mmol/l) and the other group with conventional blood glucose control targeting blood glucose of 140 to 180 mg/dl (7.7 to 10 mmol/l). The trial was terminated early because of a high rate of unplanned protocol violations. Hypoglycemic rate was more in people with tight glycemic control (8.7 versus 2.7 percent). Intensive care unit mortality rate was same in both groups (Preiser JC 2009).

In 2003 multicenter randomized trial of 18 centers done in German, The VISEP study (The Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis). It compared intensive insulin therapy targeting blood glucose levels of 80 to 110 mg/dl (4.4 to 6.1 mmol/l) with conventional glucose control targeting blood glucose level of 180 to 200 mg/dl (10 to 11.1 mmol/l), as well as comparing two methods of volume resuscitation. The patients were distributed into two groups. One group with tight glycemic control using intensive insulin therapy targeting blood glucose levels of 80 to 110 mg/d (4.4 to 6.1 mmol/l) and the other group is conventional control group targeting blood glucose levels of 180 to 200 mg/dl (180 to 11.1). The trial was stopped after 488 patients were enrolled because intensive insulin therapy substantial increased the rate of hypoglycemia (12.1 versus 2.1 percent) and serious adverse events (10.9 versus 5.2 percent). The trial then continued with only patients in the conventional

therapy group until 537 patients were enrolled. The following results were spotted when intensive insulin therapy group was compared to conventional glucose control group; the intensive insulin therapy group had mean blood glucose levels lower than conventional group (112 versus 151 mg/dL {6.2 versus 8.3 mmol/l}). Severe hypoglycemia (blood glucose less than 40 mg/dl {less than 2.2 mmol/l}) was significantly more common in intensive insulin therapy group. In 28 days, in the mortality and morbidity there were no significant difference in both groups (Brunkhorst FM 2008).

The Normoglycemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study is multicenter randomized control trial done in 2009. Patients recruited in this study were distributed into two groups. One group with tight glycemic control using intensive insulin therapy targeting blood glucose levels of 81 to 108 mg/dl (4.5 to 6 mmol/l) and the other group with conventional glucose control targeting blood glucose levels below 180 mg/dl (10 mmol/l). 6104 critically ill patients were involved in this study. The investigators found that ; the mean blood glucose levels were lower in intensive insulin therapy group (115 versus 144 mg/dL) and the 90 days mortality was pointedly higher in intensive insulin therapy group (27.5 versus 24.9 percent, odds ratio 1.14, 95 percent CI 1.02-1.28). Also mortality was significantly high in surgical patient who received intensive insulin therapy than patients on conventional therapy (24.4 versus 19.8 percent, odds ratio 1.31, 95 percent CI 1.07-1.61). as well as the study showed significant increase in cardiovascular mortality and no important difference in morbidity was ahown in both the groups in terms of renal replacement therapy or number of days of mechanical ventilation (Finfer S 2009).

Annane D and his colleagues in 2010 did a large multicenter study including 509 adults with septic shock who presented with multiple organ dysfunctions (The Corticosteroid Treatment and Intensive Insulin Therapy for Septic Shock in Adults or COIITSS). The study was designed to examine the efficacy of intensive insulin therapy in patients with septic shock and treated with hydrocortisone and to assess the benefit of fludrocortisone. Patients were randomly allocated into four groups: group one patients treated with continuous intravenous insulin infusion and hydrocortisone alone, group two patients treated with continuous intravenous insulin infusion and hydrocortisone plus fludrocortisone, group three patients treated with conventional insulin therapy and hydrocortisone alone, or group four patients treated with conventional insulin therapy and intravenous hydrocortisone plus fludrocortisone. Investigators concluded that

intensive insulin therapy did not improve in-hospital mortality among patients who were treated with hydrocortisone for septic shock when compared with conventional insulin therapy. The addition of oral fludrocortisone did not result in a statistically important improvement in in-hospital mortality (Annane D 2010).

Van den Berghe G and colleagues conducted a single center trial of 1548 patients from surgical intensive care unit (the Leuven surgical trial). They looked for the difference in mortality and morbidity in surgical critically ill patient who received intravenous insulin targeting blood glucose levels of 80 to 110 mg/dl (4.4 to 6.1 mmol/l) and surgical critically ill patient who received intravenous insulin only when blood glucose levels exceeded 215 mg/dl (11.9 mmol/l) targeting blood glucose levels of 180 to 200 mg/dL (10 to 11.1 mmol/l) . All patients involved in the trial received 200 – 300 grams of intravenous glucose during the first day of intensive care unit admission. In second day of intensive care unit admission most of the patients received parenteral nutrition added to enteral nutrition, on the second day of intensive care unit admission if necessary to achieve the caloric goal. The mean age in this study was 63 years and 71 percent were male. 63 percent of the patients underwent cardiac surgery. The mean Acute Physiologic and Chronic Health Evaluation [APACHE II] score was 9 which reflects that patient were not severely ill. The following outcomes were detected: in intensive insulin therapy group the mean blood glucose was significantly lower (103 versus 153 mg/dl {5.7 versus 8.5 mmol/l}). The mortality in intensive care unit in patients whom assigned to intensive insulin therapy was significantly less (4.6 versus 8 percent) and patients on intensive insulin therapy who stayed 5 days or more in intensive care unit benefit more than others. Tight glycemic control by using intensive insulin therapy significantly reduced the hospital mortality (7.2 versus 10.9 percent). Also the study detected that morbidity was reduced in tight glycemic control group; critical illness polymyoneuropathy, acute renal failure, transfusion requirement, and blood stream infections all were less in intensive insulin therapy group. Blood glucose of less than 40 mg/dl (less than 2.2 mmol/l) which defines the hypoglycemia was more frequent in intensive insulin therapy group (5.1 versus 0.8 percent). The mortality rate was high in control group and this was the main concern in this study, the intensive care unit mortality in control group was 8 percent and hospital mortality was 11 percent. This mortality rate higher than the mortality rate recorded for most patients undergoing routine cardiac surgery (van den Berghe G 2001). This high death

Table (4) Characteristics of randomized controlled trials included in this review

Study	NP	RA%	MA	D%	FD	ITV	TBG	OutComes
Van den Berghe et al.(surgical ICU)	1548	Cardiac surgery, 63	62.8	13	Hospital stay	Both groups: insulin infusion	CG: 10–11.1 TG: 4.4–6.1	Mortality, hypoglycemia, new need for dialysis, sepsis
Van den Berghe et al.(medical ICU)	1200	Respiratory, 42.7; gastrointestinal, liver, 25.5	63.5	17	90 days	Both groups: insulin infusion	CG: 10–11.1 TG: 4.4–6.1	Mortality, hypoglycemia, new need for dialysis, sepsis
Arabi et al.	523	Medical: 83 Surgical: 17	52.4	40	Hospital stay	Both groups: insulin infusion Mean BG	CG: 10–11.1 TG: 4.4–6.1	Mortality, hypoglycemia, new need for dialysis, sepsis
Brunkhorst et al.	537	Medical: 47 Surgical: 53	64.6	30	90 days	Both groups: insulin infusion Mean morning	CG: 10–11.1 TG: 4.4–6.1	Mortality, hypoglycemia, new need for dialysis
NICE-SUGAR Study	6104	Medical: 62 Surgical: 38	62.2	20	90 days	Both groups: insulin infusion	CG: b10 TG: 4.5–6.0	Mortality, hypoglycemia, new need for dialysis, sepsis
Glucontrol study	1101	Medical: 40 Surgical: 47 Trauma: 13	64	18	Hospital stay	Both groups: insulin infusion Median BG	CG: 7.8–10.0 TG: 4.4–6.1	Mortality, hypoglycemia
COIITSS study	509	Medical: 75 Surgical: 11	64	NA	180 days	CG: insulin infusion or subcutaneous insulin injection TG: insulin infusion	CG: not defined TG: 4.4–6.1	Mortality, hypoglycemia

NP= Number of Patients RA = Reason for Admission %, MA Mean Age, D% = Diabetes %, FD= Follow up Duration, ITV = Intervention, TBG = Target Blood Glucose, TG = Tight Glycemic Control and CG = Conventional Glycemic Control.

rate in control group promotes the likelihood that there was a harmful intervention in the control group that was improved by intensive insulin therapy. One option is that the large glucose load administered on the first two days in intensive care unit, well tolerated in intensive insulin therapy group because of aggressive insulin therapy and it was harmful to the control group (Likosky DS 2006).

These outcomes were reinforced by a meta-analysis of five randomized trials of 1972 patients that compared tight glycemic control by using intensive insulin therapy targeting blood glucose levels of less than 150 mg/dl (less than 8.3 mmol/l) to conventional control in surgical intensive care unit patients. Patients who received intensive insulin therapy had significantly lower mortality than those who received less conventional glycemic control (7.4 versus 11.8 percent, relative risk 0.63, 95 percent CI 0.44-0.91). However, the results of the meta-analysis were largely driven by the Leuven surgical trial, an important limitation (Griesdale DE 2009).

The same group who performed the Leuven surgical trial did a similar trial totally in critically ill medical patients. 1200 patients randomly assigned to one of two groups. One group patients with tight glycemic control using intensive insulin therapy targeting blood glucose levels of 80 to 110 mg/dL (4.4 to 6.1 mmol/l) and the other group patients with conventional glycemic control targeting blood glucose levels of 180 to 200 mg/dL (10 to 11.1 mmol/l). The insulin infusion protocols and nutritional strategies were the same as the Leuven surgical trial intensive. The study spotted the following; the patients on intensive insulin therapy had the mean blood glucose lower than patients with conventional glycemic control (105 versus 160 mg/dL {5.8 versus 8.8 mmol/l}). The overall hospital mortality was not significantly changed by intensive insulin therapy (37.3 versus 40 percent in the control group). Intensive care unit length of stay, hospital length of stay, duration of mechanical ventilation, and acute kidney failure were significantly reduced by intensive insulin therapy. Hypoglycemia was significantly more common in the intensive insulin therapy group (18.7 versus 3.1 percent) (Van den Berghe G 2006). Like the Leuven surgical trial, the nutritional approach in the Leuven medical trial is not the standard of care worldwide. As a result, it is uncertain whether the results of this trial are generalizable to patients who receive a more usual nutritional approach, such as enteral nutrition started early and increased over the first few ICU days (Heyland DK 2003).

From the above mentioned studies which compare two targets of blood glucose levels tight glycemic control versus conventional control in intensive care unit patients only the Leuven surgical trial concluded that tight glycemic control in interventional group significantly reduce mortality but the other interventional studies failed to re-conclude that and had been shown increase mortality in tight glycemic control group. Here the question comes why the studies after the Leuven surgical trial did not show the same result. This difference in results could be related to the incidence of severe hypoglycemia in interventional groups of randomized trials (van den

Berghe G 2006, Brunkhorst FM, E 2008) and there was strong and independent relation between hypoglycemia and increased mortality as demonstrated by observational and interventional studies (Vriesendorp TM 2008, Krinsley JS 2011). The risk and benefits of tight glycemic control could be affected by many variables like disease severity, different protocols, different glycemic targets, different definitions of hypoglycemia and different underlying comorbidities. Blood glucose variability is another possibly important factor that may impact patient outcome with insulin therapy. The increased width of fluctuations in blood glucose concentration increases risk of mortality and morbidity as shown in the clinical trials (Ali NA 2008).

One could list many explanations as to why the given five negative randomized control trails have not shown any beneficial effect when it comes to the application of tight glycaemic control, except for the assumptions that the tight glycaemic control might not have been beneficial to the specific intensive care unit patients **(**Vlasselaers D 2009). Thus this could have brought in a variability in the effectiveness of tight glycaemic control, and the known differences as seen in the trial designs, along with modification of the standard of care, timing variance in tight glycaemic control, and the linkage among the intervention groups and control groups when it comes to the blood glucose levels which have been noticed in the successive randomized control trail **(**Vlasselaers D 2009). It can be said that the tight glycaemic control is a complex intervention which has to be applied in many a sequential steps which have many a potential sources of variability (Vlasselaers D 2009). One can also study the Methodological aspects which are related to the tight glycaemic control, and could be a potential source of variability when it comes to the effectiveness of the given strategy. One could categorize the Items in the following subjects which are monitoring, algorithm, insulin delivery, and experiences **(**Vlasselaers D 2009). Items could be positioned on a line which could vary from the easy, simple, distinct or clear to implement and could extend to obscure, indistinct, complex or difficult when one comes from one centre to another **(**Vlasselaers D 2009).

When one looks at the positive randomized control trail which have been studied form Leuven, it has been seen that the intensive care unit nurses did have accurate blood gas analysers which were used to measure blood glucose as was in the arterial blood **(**Vlasselaers D 2009). The same was done in strict time points. Also it has been seen that in the second randomized control trail from Leuven there is a variety of glucose analyzers along with blood gas analyzers which have been given due consideration **(**Vlasselaers D 2006). Tight glycaemic control group also had a

continuous infusion of insulin which was done exclusively through the central venous line, with the help of the accurate syringe-driven infusion pumps. Also Delicate insulin dose adaptations had been performed. (McCowen KC 2001). The same have been undertaken by the intensive care unit nurses who have been trained to implement this complex strategy which is the insulin dose adaptations.The same was but done on a guidance and was targeted at blood glucose levels which were close to the lower normal limit, and needed a high level of decision making (McCowen KC 2001). Another aspect which was crucial in this context was the training of intensive care unit nurses which was restricted to the training sector of prevention of hypoglycaemia . Most challenging would be the 'expertise-based control system' which could also be taken into account when it comes to the intensive care unit nurses from Leuven (McCowen KC 2001). Also when one looks at the algorithm from Leuven it can be seen that the same contains just a set of simple rules (which could be said to be the explicit rules, like the ones in the closed-loop systems, with the computer-based decision support systems, along with the paper-based systems which make use of sliding scales) (McCowen KC 2001). The same then needs an intuitive decision making which has been done by the users. Also it is crucial to analyse the specific elements in the given 'intuitive control system' which bring out the outcome which have been relevant in the study trials from Leuven. This could also be used for the skill and motivation which pertains to the intensive care unit nurses from the Leuven study. Also the nurse's talent in the implementation process of tight glycaemic control, could be used in the studies which have been done beyond their intensive care unit (McCowen KC 2001). This brought in a 29 percent lower mortality in comparison to the conventionally treated group.

Three domains of glycemic control in critically ill patients (hyperglycemia, hypoglycemia and glycemic variability) is the result after these finding and must be addressed to optimize glycemic control in critically ill patient. In 2006 Egi M and his colleagues extracted blood glucose values from electronically stored biochemical databases and of data on patient's characteristics, clinical features, and outcome from electronically stored prespectively collected patient databases and they calculated the Standard Deviation of glucose as a marker of variability and of several indices of glucose control in each patient; and statistical assessed the relation between these variables and intensive care unit mortality. By Using multiple variable logistic regression analysis, both mean and Standard Deviation of blood glucose were significantly associated with intensive care unit mortality ($P < 0.001$; odds ratios [per 1 mM] 1.23 and 1.27, respectively) and

hospital mortality (P < 0.001 and P = 0.013; odds ratios [per 1 mM] 1.21 and 1.18, respectively) (Egi M 2006) .

In a retrospective analysis of a cohort of ventilated, critically ill surgical and trauma intensive care unit patients placed on an automated insulin protocol was performed by Dossett LA and his group 2008. Blood glucose variability was measured by comparing standard deviation, percentile values, successive changes in blood glucose, and by calculating the triangular index for various glucose-related indices. Eight hundred and 58 patients had 46,474 blood glucose and insulin dose data points. 121 patients died for an overall mortality rate of 14 percent. Several measures of blood glucose variability (maximum successive change in blood glucose and the triangular index) were different between the groups despite similar mean blood glucose between survivors (117 mg/dL {6.50 mmol/l}) and non-survivors (118 mg/dL {6.55 mmol/l}). Increased blood glucose variability is associated with mortality in the surgical ICU (Dossett LA 2008).

Al-Dorzi HM and his group (2010) in his nested-cohort of 523 patients evaluated the predictors of glycemic fluctuation and its association with critical care outcomes. The patients from medical and surgical intensive care units were randomized to either tight glycemic control targeting blood glucose levels of 80 to 110 mg/dl or conventional glycemic control targeting blood glucose levels of 180 to 200 mg/dl. Glycemic fluctuation was defined as the mean difference between the highest and lowest daily blood glucose. Patients were divided into wide and narrow fluctuation groups according to the median glycemic fluctuation (108 mg/dl). Predictors of glycemic fluctuation were age, diabetes mellitus, and daily insulin dose. Similar levels of glucose fluctuation were observed in tight glycemic control patients and conventional glycemic control patients. Wide glycemic fluctuation was associated with higher mortality (22.2 vs. 8.4%, P < 0.001). they conclude that, wide glycemic fluctuation is an independent predictor of mortality in critically ill patients. Whether reducing glycaemic fluctuation would lead to better outcomes and needs further evaluation (Al-Dorzi HM 2010).

Mackenzie I and colleagues investigated 3434 critically ill patients admitted over one year to four separate ICUs: surgical-liver; trauma-medical; cardiac surgical; neuro-science in large observational single center trial. Measures of central tendency, blood glucose variability and hypoglycemia and their association with mortality are the three separate domains of glycemic control recognized in this trial. Each of different domains of glycemic control affected mortality

independently and that the effects of derangements in more than one domain were additive as mentioned by Mackenzie I (Mackenzie I 2011). Increasing glycemic variability was steadily associated with increasing mortality and the domain reflecting hypoglycemia was inversely related to mortality, with highest mortality among patients in the lowest quintile of minimum glucose (Mackenzie I 2011)

James S Krinsley and his group (2013) examined data of 44964 patients who were admitted to 23 intensive care units from nine counties between February 2001 and May 2012 retrospectively. They observed the relation between the three dominions (hyperglycemia, hypoglycemia and blood glucose variability) and diabetes status to mortality. They concluded that each part of the three dominions was independently associated with increase mortality in critically ill patients and diabetic status modifies these relations. They stated that higher glucose range may benefit patients with diabetes if compared to those patients without diabetes. In addition to that regardless the diabetic status hypoglycemia was risk factor to increase mortality. Additionally increase blood glucose variability independently associated with increased mortality among patients with diabetes (James S Krinsley).

In a summary as mentioned in above evidence, tight glycemic control targeting normo-glycemia in critically ill adult patients associated with increased mortality while blood glucose target of 140 to 180 mg/dL (7.8 to 10 mmol/l) minimizing the complications of hyperglycemia and the risk of hypoglycemia and it is sequences. The blood glucose levels greater than 180 mg/dl (10 mmol/l) is associated with poor outcome as mentioned in clinical trials. Also as stated in above trails the intensive insulin therapy targeting blood glucose levels of 80 to 110 mg/dl (4.4 to 6.1 mmol/l) most of time is associated with increased risk of hypoglycemic which in some studies increases the mortality rate and in the other studies did not affect the mortality rate. Avoidance of major blood glucose fluctuation as stated in above trials improves mortality. Blood glucose monitoring cautiously is essential to achieve the target range safely and to avoid hypoglycemia.

Chapter 7

Impact of Hypoglycemia on Critical Ill Patients

Hypoglycemia is the most common adverse effect of intensive insulin therapy targeting tight glycemic control. Hypoglycemia defined as blood glucose of less than 40 mg/dl (2.2 mmol/l) It occurs in up to 19 percent of patients treated with intensive insulin therapy (Van den Berghe G 2006), or when defined as a blood glucose of <60 mg/dL (3.3 mmol/l) It occurs in up to 32 percent of patients treated with intensive insulin therapy (Grey NJ 2004). If Hypoglycemia frequently occurs is problematic because it can lead to seizures, brain damage, depression, and cardiac arrhythmias. Hypoglycemia is also a risk factor for death (Preiser JC 2009). The low blood glucose levels will lead to activation of counter-regulatory response, this response maximize the autonomic nervous system function which will elevate the blood glucose levels, this happen through increased secretion of catecholamine (Cryer PE 1997, McAulay V 2001). The Catecholamine augment peripheral insulin resistance, glycogenolysis, gluconeogenesis and lipolysis as well Catecholamine will diminish the glycolysis so peripheral tissue will consume less glucose and the glucose will shift to organs which depends on it as a source of energy. Because of autonomic nervous system patient with hypoglycemia will have non-specific clinical manifestation like increased blood pressure, tachycardia, numbness, anxiety and sweating. If the hypoglycemia becomes more severe the patients will suffer from neurological symptoms like seizures, loss of consciousness and permanent brain damage and even death. In critically ill patients because of pathophysiological changes and medication like sedation the above mentioned clinical manifestation may not present (Cryer PE 1997, McAulay V 2001). The amount of ketone body, the duration of hypoglycemic episode and severity of episode may affect the risk of mortality. If the ketone body level is bigger this will help as alternative energy source for the brain during hypoglycemic episode and will increase the brain tolerance to hypoglycemia which may reduce the mortality (Gordon SM 2008). There are number of factors made in intensive care unit patient at increased risk of hypoglycemia, the counter-regulatory mechanisms are loaded by the disease, exposing patients to an increased risk for hypoglycemia. Glucocorticoid and catecholamine levels are already high in the critically ill patients and more rises in response to hypoglycemia might be impossible or insufficient to compensate for hypoglycemia. Beta-blockers, aspirin, oral hypoglycemic drugs and octreotide are associated

with hypoglycemia. Additionally mechanical ventilation and veno-venous hemofiltration are associated with an increased risk of hypoglycemia (Krinsley JS. 2008).

Hypoglycemia may increase mortality by means of impairment of autonomic function, alteration of blood flow and composition, white blood cells activation, vasoconstriction, and the release of inflammatory mediators and cytokines (Wright RJ 2008) Severe hypoglycemia may also be associated with a prolonged QT interval (Gill GV 2009) which confers a predisposition to potentially fatal cardiac arrhythmias.

Before the era of tight glycemic control hypoglycemia incidence in intensive care unit was difficult to estimate. Griesdale DE (2009) in his meta-analysis of randomize controlled trials find that patients on tight glycemic control had six fold increase in incidence of hypoglycemia than patients on conventional control (1.5 percent vs. 10 percent) and the increase in incidence was related to the severity of the illness (Griesdale DE 2009). The recognition of hypoglycemia in intensive care unit patient might be deferred because of masked clinical signs and symptoms and the diagnosis of hypoglycemia in critical care patients centered on blood glucose measurements.

Hypoglycemia in critically ill patients is related to increase mortality and poor outcome but the question is the hypoglycemia happen in the sick patients and so considered as a marker of the disease severity rather than is causally linked to harm (Krinsley JS 2007).

Hypoglycemic risk increased with tight glycemic control in critically ill patients in surgical and medical intensive care unit as reported by Van den Berghe et al and he stated that patients in medical intensive care unit had a worse prognosis. In addition he did not mark hypoglycemia as an independent risk factor for a poor prognosis (Van den Bergh G 2006). Vriesendrop and colleagues in their study found same as Van den Berghe et al and they found two cases of hypoglycemia associated coma occurring after implementing a tight glycemic control protocol. In both cases, coma was finally explained by the medical condition. However, an effect of hypoglycemia cannot precisely be ruled out. Seizures were also detected in two patients, one treated with tight glycemic control protocol and one had a spontaneous hypoglycemia without being treated with a tight glycemic control protocol. These data suggest that adverse neurological events after hypoglycemia are not always associated with tight glycemic control or impaired neurological long-term outcome. In fact they interpret hypoglycemia rather a marker of severity of illness than as a harmful event.

Brunkhorst and colleagues in their multi-center study (VISEP) pointed out that hypoglycemia as an independent risk factor for increased mortality (Brunkhorst FM 2008). GluControl trial was terminated because of a high incidence of hypoglycemia ,and hypoglycemia tended to be connected to worse prognosis. Hypoglycemia was 14 times more in critically ill patient treated with tight glycemic control as compared with patients treated with conventional control in the multi-center NICE-SUGAR study. The NICE-SUGAR Study Investigators did post hoc analysis of the NICE-SUGAR study database showed that the number of patients who had severe hypoglycemia 223 patients (3.7 percent) 93.3 percent of them were on tight glycemic control and the number of patients who had moderate hypoglycemia 2714 patients (45 percent) 82.4 percent were on tight glycemic control. The risk of death was increased among the patients with moderate hypoglycemia and severe hypoglycemia and the association exhibits a dose–response relationship. Moderate hypoglycemia was associated with an increase in the risk of death of 40 percent, and severe hypoglycemia with a doubling of the risk. The associations were consistent across and the subgroups of patients we examined. For both moderate and severe hypoglycemia, the association was strongest for death from distributive shock. In addition, the association was stronger among patients with severe hypoglycemia than among those with moderate hypoglycemia, and was stronger among those with moderate hypoglycemia that occurred in more than 1 day than among those with moderate hypoglycemia in only 1 day. Krinsley and colleagues in their retrospective database review of a mixed medical and surgical intensive care unit find that hypoglycemia as an independent predictor for mortality. In the same study, also the variability of blood glucose levels has been identified as a strong independent predictor of mortality (Krinsley JS 2013).

In summary, clinical signs of hypoglycemia are masked in the intensive care unit setting, the diagnosis of critical hypoglycemia is often delayed. Since the hypoglycemia persisting over a longer time appears to be a possible independent risk factor for mortality and morbidity. However, besides hypoglycemia, hyperglycemia and fluctuations of blood glucose levels are associated with long-term neurocognitive dysfunctions and with an increased mortality. Tight glycemic control increases the risk of hypoglycemia in the critically ill patients. However, appropriate protocols can reduce this risk substantially.

Chapter 8

Conclusions

Hyperglycemia is a common event in critically ill patients and obviously as shown in clinical trials, hyperglycemia is related to increase mortality and morbidity in critically ill patients. Critically ill patients with blood glucose more than 200 mg/dl (11.1 mmol/l) are more susceptible to infection and they spent more days in intensive care unit as well as hyperglycemia in critically ill patients can cause volume and electrolyte disturbances mediated by osmotic diuresis.

Treatment of hyperglycemia associated reduction of mortality, wound infection and less days in intensive care unit are evident in clinical trials. Insulin is the drug of choice for management of hyperglycemia in critically ill patients. The IV infusion insulin is the safest way to control the blood glucose in critical patients if it is accompanying with close monitoring of blood glucose.

The main question in our study was to which extent the blood glucose has to reduce. Tight glycemic control which means targeting blood glucose levels of 80 to 110 mg/dl (4.4 to 6.1 mmol/l) was associated with lower mortality and morbidity and no significant increase in severe hypoglycemia was concluded by Leuven surgical trails in 2001. But later trails failed to prove that tight glycemic control could decrease mortality and morbidity in critical ill patients and was associated with increased risk of severe hypoglycemia and mortality rate. Blood glucose target of 140 to 180 mg/dl (7.7 to 10 mmol/l) as revealed by clinical trials was related to lower risk of hypoglycemia and mortality if compared with tight glycemic control. On the other hand blood glucose variability was related to increase mortality as shown in clinical observations. Improving patient's outcome and safety are our targets, so by avoidance of hyperglycemia and decreasing blood glucose variability will improve the outcome and by avoidance of hypoglycemia will improve safety. According to the evidence reviewed in our study we recommend Keeping blood glucose level between 140 and 180 mg/dl (7.7 and 10 mmol/l) with blood glucose variability as less as we can and we recommended avoiding tight control to decrease the risk of hypoglycemia. Close monitoring of blood glucose by using accurate measurement technique and use of validity insulin protocols are very important factors to provide safety to our patients.

Finally we need further multicenter trials including a larger number of patients to define the optimal blood target in critically ill patients and to confirm the benefit effect of blood glucose targets from 140 to 180 mg/dl (7.7 to 10 mmol/l) in critically ill patients.

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