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ABSTRACT

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I. INTRODUCTION

Hyperglycaemia in the hospitalized patients has gained attention due to its association with prolonged hospital stay, increased morbidity and mortality in inpatient.[1] This association has been established for acute conditions like myocardial infarction, Stroke, pneumonia acute trauma or burn.[2] In the last 14 years glycemic goals have changed within the hospital setting. Various degrees of glycemic control have been studied and a recent consensus statement from ADA/AACE recommends a target glucose range of 140-180mg/dl in most hospitalized patients.[3] Stress hyperglycemia historically was felt to be part of the natural course of acute illness and defined as a blood glucose level>140 mg/dL without a previous history of diabetes or glycated hemoglobin (HbA1c) >6.5%.[4] In the largest review of Hospital glucose data of more than 126 U.S hospitals, 46% of all Blood sugars in the ICU setting and 31.7% of all blood sugars in non ICU patients were in the hyperglycemic range.[5] Several studies including large trials, have shown that admission hyperglycemia is a risk factor for poor outcome following focal and global cerebral ischemia.[6]

The prevalence of admission hyperglycemia (glucose levels of>140 mg/dL) in different epidemiological studies ranges from 51% to >58% of patients admitted with acute myocardial infarction. A study reported hyperglycemia in up to 50% of patients with acute MI whereas previously diagnosed Diabetes was found only in 20% to 25% of patients.[7] The relationship between glycemic control and the severity of sepsis was analyzed in a cohort of 191 patients concluded that patients with hyperglycemia has longer length of stay as compared to those with normal blood sugars.[8] A meta-analysis of over 26 studies, including the largest, Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR), showed decreased morbidity and mortality in patients with moderately controlled hyperglycemia.[9] Impaired glycemic control are associated with increased rates of infections, morbidity, and mortality, and increases hospital length of stay (LOS).[10] [11] All prior studies have worked on

hyperglycemia and its impact on morbidity and mortality, less work has been done to evaluate effect of hyperglycemia on average length of stay.

All prior studies have worked on hyperglycemia and its impact on morbidity and mortality, less work has been done to evaluate effect of hyperglycemia on average length of stay. Purpose of this study will be to assess how glycemic control impacts on length of stay of patients in tertiary care hospital. Additionally we want to see if non-diabetics who have hyperglycemia differ in outcomes at the end on length of inpatient stay.

Despite advances in the management of patients with diabetes mellitus (DM), this population still has a poorer prognosis after ischemic events compared with nondiabetic patients. Stress hyperglycemia can be defined as a blood glucose level >140 mg/dL without a previous history of diabetes or glycated hemoglobin (HbA1c) >6.5%.[13] Although the Diabetes Insulin Glucose in Acute Myocardial Infarction (DIGAMI) trial and studies conducted in Leuven demonstrated the benefit of intensive glucose control in critically ill patients, later studies failed to replicate these findings.[14,15] It is difficult to define the incidence of acute hyperglycemia, which may vary from 40-90%, depending on the threshold used to define abnormal levels of glucose.[12,16] Hyperglycemia in the critical care setting is associated with a poor prognosis in patients with no history of DM. This association is well documented for both admissions and the mean glucose level during the hospital stay. In a prospective cohort study that evaluated patients with community-acquired pneumonia, increased blood glucose levels on admission were associated with increased mortality in patients with no history of diabetes.[17] The worldwide prevalence of diabetes is 2.8%. This rate increases to approximately 15-30% among critically ill patients.[12,13] In patients with pre-existing DM, the presence of hyperglycemia has not been consistently associated with a worse prognosis. Patients with diabetes exhibited increased mortality in a cohort of patients with community-acquired pneumonia, but this outcome was not influenced by the levels of glucose on admission.[17]

Hyperglycemia can be seen in various settings, Postoperative period, in a study of 263 patients undergoing vascular surgery, intensive glucose control was associated with a reduction in the composite endpoint of all-cause death, myocardial infarction, and acute heart failure. Moderately strict blood glucose control (target range 110-150mg/dl) throughout the hospital stay, added to the usual standard of care in patients undergoing heart surgery, was associated with a 6% reduction in infection rates and a 12% reduction in atrial fibrillation, with no between-group differences in mortality. However, other studies have failed to show any benefit, even in this subgroup of patients.[18]

Neuro-critical patients, in a study of 933 patients with an admission diagnosis of stroke, strict glucose control was not beneficial in reducing mortality or improving neurological outcomes.

However, this study was ended prematurely due to difficulties in enrollment, thus limiting its statistical power. These findings were replicated in a later study, which compared aggressive blood glucose control (target range <130mg/dL) with conventional control (target <200mg/dL) in 46 patients with ischemic stroke. However, in another study of acute ischemic stroke patients who developed hyperglycemia and did not have a previous history of diabetes, intensive glucose control was associated with improved 30-day neurological performance, as measured by the National Institutes of Health Stroke Scale (NIHSS) score, compared with performance following conventional blood glucose control.[19] In a meta-analysis that included studies on only neurocritical patients, strict glycemic control had no impact in mortality, although a less strict glycemic target (140-180mg/dL) was associated with fewer unfavorable neurological outcomes.[20]

Myocardial infarction, it is not known whether intensive blood glucose control is associated with better outcomes in patients with acute myocardial infarction (AMI). In the DIGAMI trial, patients were randomized to receive either an insulin/glucose infusion during the first 24 hours after admission, followed by subcutaneous administration of intermediate- and short-acting insulin four times daily for at least 3 months, or standard DM treatment at the discretion of their care providers. High cardiac risk was defined as

meeting two or more of the following criteria: age ≥70 years, a history of previous AMI, a history of congestive heart failure, and ongoing digitalis treatment. The patients were classified into four predefined strata according to their history of insulin use and their cardiac risk: 1, no insulin and low risk; 2, insulin and low risk; 3, no insulin and high-risk; and 4, insulin and high risk. All other aspects of AMI management were similar between the two groups. Although patients in the intervention group (who received the insulin/glucose infusion) had a slight reduction in in-hospital mortality (9.1% versus 11.1%; non-significant) and 3-month mortality (12.4% versus 15.6%; nonsignificant), only 1-year mortality was significantly lower in the intervention group (18.6% versus 26.1%; relative mortality reduction, 28%; 95% CI, 8-45%), questioning whether the benefit was due to acute management in the ICU or to later intensive control. An analysis of mortality in the pre-stratified risk groups showed that the greatest reduction occurred among patients with no prior insulin treatment. In this group, the relative reduction in mortality was 51% (19-70%; p=0.004) at the 1-year follow-up. [21]A meta- analysis of 11 randomized clinical trials including over 23,000 AMI patients showed no benefit for the use of intensive glucose control protocols.[22]

In sepsis, the relationship between glycemic control and the severity of sepsis was analyzed in a cohort of 191 patients treated with intensive glucose control (target of 80-140mg/dl). The researchers concluded that among patients with severe sepsis or septic shock, the risk of hypoglycemia and hyperglycemia was higher. In a multicenter randomized trial (the Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP study), conventional therapy was compared with intensive insulin therapy, and fluids for resuscitation (10% pentastarch versus modified Ringer's lactate) were also compared. There was no benefit for strict glucose control in patients with severe sepsis, and the trial was stopped early for safety reasons, given the high rate of hypoglycemia. In the NICE-SUGAR trial, an analysis of subgroups did not show any improvement in mortality in patients with severe sepsis. The Surviving Sepsis Campaign Guidelines recommend starting insulin therapy after two consecutive blood glucose measurements above 180mg/dl and an upper target level ≤180mg/dL.[23]

The administration of vasopressors, corti-costeroids, and enteral and parenteral nutrition, as well as the discontinuation of this therapy due to a variety of procedures, leads to significant variability in blood glucose levels. Retrospective studies have shown a relationship between increased blood glucose variability and increase mortality. A retrospective analysis of the Leuven dataset showed that patients with the greatest blood glucose fluctuations had the worst outcomes, regardless of allocation within the study.[24] The optimal method to measure the amplitude of blood glucose levels is not defined. In a systematic review, 13 different indicators were reported, without a clear definition of the best method for the assessment of glycemic variability. However, a prospective cohort study evaluated the standard deviation and mean amplitude of the glycemic index, the absolute glucose change per hour, and the glycemic lability index. The standard deviation was the only measure that was consistently associated with hospital mortality.[25] Further clinical trials are required to determine whether the use of indices of glucose control variability in critically ill patients can reduce morbidity and mortality.

A need for an assessment of baseline blood glucose prior to ICU admission by HbA1c measurement has been suggested, particularly in patients with no history of DM. In hospitalized patients with random admission, hyperglycemia with HbA1c >6% had a specificity of 100% for the diagnosis of diabetes and a sensibility of 57%.[26] Acute hyperglycemia does not appear to be a marker of mortality in critically ill patients with pre-existing DM.

II. PATHOGENESIS OF THE STRESS HYPERGLYCEMIA

Severe sepsis, systemic inflammatory response syndrome (SIRS), and traumatic brain injury (TBI) are conditions associated with significant morbidity and mortality. Hyperglycemia is often a consequence of these three related conditions. Although the first steps in response to severe infections (sepsis), severe tissue damage (SIRS),

and brain injury subsequent to trauma (TBI) vary, the later steps, which lead to morbidity, multi-organ failure and death, seem to be very similar.[27]

In the initial phases of these three conditions, there is a very strong inflammatory response, with high levels of IL-1β, TNFα, and IL-6, among other cytokines and chemokines, being secreted by M1-type macrophages and others. In this initial pro-inflammatory stage of these critical illnesses, very high levels of blood glucose (hyperglycemia) are often observed in these Patients.

Hyperglycemia, even in non-diabetic patients, is a hallmark of these conditions in their initial phase but is also a prognostic indicator, with a general correlation between glucose blood levels and the outcomes of morbidity and death. Glycemic control in the critically ill also affects the immune system with general attenuation of immune function which might avoid unnecessary inflammation in TBI but could prove disastrous in sepsis. Here we discuss molecular mechanisms leading to hyperglycemia in critically ill patients.[28]

III. METABOLIC CHANGES IN HYPERGLYCEMIA

If hyperglycemia is at least partially consequent to a shift in glucose metabolism and insulin resistance, then what does that imply for the treatment of hyperglycemia in critically ill patients? Although insulin treatment may constitute part of the therapy, is it not better to try insulin treatment in combination with new therapies that could possibly redirect the altered glucose metabolism in these cells? Recent advances in understanding the role of aerobic glycolysis in critically ill patients suggest novel mechanisms contributing to hyperglycemia and, as a result, novel approaches to therapy. One of the first important recent findings was the identification of increased succinate in macrophages stimulated by the pro-inflammatory compound lipopolysaccharide (LPS). These authors conducted a thorough metabolomic study of this inflammatory pathway and confirmed the stimulation of glycolysis and inhibition of oxidative phosphorylation. Succinate was elevated some 30-fold during LPS stimulation. Succinate is transported from the mitochondria (where most of the excess is formed through anaplerosis via stimulation of glutamine transformation to α-ketoglutarate, the precursor to succinate in the TCA cycle) to the cytoplasm, where it inhibits prolyl hydroxylase, the enzyme that acts on HIF-1α and leads to its normal fast protein turnover. Inhibiting prolyl hydroxylase stabilizes HIF-1α and leads to aerobic glycolysis (the Warburg Effect).[36]

Before we investigate more deeply into the hyperglycemia and hyperlactatemia observed in critically ill patients, we ask whether it is justifiable to treat hyperglycemia (and hyperlactatemia) as one entity in sepsis, SIRS, and TBI. The literature is somewhat confusing on this point. We have already mentioned that the original correlation of hyperglycemia and increased mortality came from patients treated in a surgical ICU and were often cardiac or thoracic surgical patients. When the same group reported on patients treated in a medical ICU, they found that intense insulin therapy to lower glucose levels decreased morbidity but not mortality. A meta-analysis of patients from five different ICUs (medical, cardiothoracic surgery, cardiac, surgical, and neurosurgical) in one large medical center showed differences in mortality when patients were very hyperglycemic among the five units. Laird and colleagues found that early hyperglycemia ([glucose] >200 mg/dL) in trauma patients led to increased mortality rates independent of the type of injury sustained.[37] TBI patients also have worse outcomes, including increased mortality, when they are severely hyperglycemic ([glucose] >200 mg/dL) on admission to an ICU. A more recent study not only confirmed this relationship but also related the prognostic capacity of initial glucose levels to the prognostic capacities of both the initial Glasgow Coma Scale (GCS) score and the Apache II score. Interestingly, initial mean glucose concentration was a better prognostic indicator for survival than either GCS or Apache II scores. Nonetheless, there are some unique properties of glucose metabolism in the brain. The glucose transporter GLUT-1 is the major transporter of glucose for non-neuronal cells (astrocytes, microglia, and oligodendroglia) and is also part of the endothelial blood-brain barrier. The GLUT-3

transporter seems to be the major source of glucose transport into brain neuronal cells. During glycolysis, accumulated lactate is shuttled between non-neuronal cells and neurons, using two different monocarboxylate transporters (MCTs) to effect this: MCT1 in endothelial and non-neuronal cells and MCT2 in neurons. Although the precise metabolism of lactate in the brain is still somewhat controversial, it is not important for further consideration here. The contribution of increased lactate to poor outcomes in TBI and the consideration of the biochemical targets that might overcome such outcomes seem to be no different than for sepsis and SIRS.[38]

IV. DIAGNOSIS

Stress hyperglycemia generally refers to transient hyperglycemia during illness and is usually restricted to patients without previous evidence of diabetes. For the purpose of this Seminar, we will discuss physical—rather than psychological—stress. However, the identifi- cation of such patients is complex. No guidelines specifically define stress hypergly- cemia. In a technical review written by the Diabetes in Hospitals Writing Committee of the American Diabetes Association (ADA), patients are classified into one of three groups—known diabetes, newly diagnosed diabetes, and hospital-related hyperglycemia (panel). This classification needs information from hospital follow-up that is not usually available. Change in glucose from baseline and not the absolute glucose concentration might be of value, irrespective of whether a patient has pre- existing diabetes. Thus, we propose two diagnostic categories of stress hyperglycemia—hospital- related hyperglycemia according to the ADA consensus definition (fasting glucose >6·9 mmol/L or random glucose >11·1 mmol/L without evidence of previous diabetes), and pre-existing diabetes with deterioration of preillness glycemic control. The most appropriate cutoff point for stress hyperglycemia in patients with pre-existing diabetes needs to be established, but certainly a patient with a well-controlled (<7%) glycosylated hemoglobin (HbA_{1c}) whose glucose concentration is consistently higher than the threshold defined for hospital-related hyperglycemia would qualify.[45] 30% of people who have diabetes in the USA are unaware of their status and, therefore, many hospitals in patients with apparent stress hyperglycemia have underlying diabetes or prediabetes. In an undifferentiated hospital population, results from a small study showed that 60% of patients with admission hyper-glycemia had confirmed diabetes at 1 year. Another study showed that nearly one in five adult inpatients had probable unrecognized diabetes—identified by an admission HbA_{1c} higher than 6·1%. In this study, random glucose concentrations poorly predicted elevated HbA_{1c}, indicating the need for more sophisticated diagnostic criteria than are available.[46,47]

Poor Outcomes related to Stress Hyper-glycaemia: One retrospective review of 1886 unselected hospital inpatients were stratified according to whether patients had normogly-cemia, pre-existing diabetes, or newly diagnosed hyperglycemia (fasting glucose >7 mmol/L or random glucose >11·1 mmol/L on two separate occasions). Compared with patients with normoglycemia, after adjustment for age, body-mass index, sex, hyper tension, coronary artery disease, infection, renal failure, and ICU admission, mortality was 18·3 times higher in patients with newly diagnosed hyperglycemia ($p<0·05$), but only 2·7 times higher in those with known diabetes ($p<0·05$). This study did not distinguish between a new diagnosis of diabetes and transient stress hyperglycemia.

However, a relation between short-term glycemic control and hospital outcomes has been identified. Patients with hyperglycemia without known diabetes who were critically ill or had acute coronary or cerebro-vascular events were shown to have increased risk of mortality, although patients who were hyperglycemic with known diabetes did not.

In post analysis, data from a large randomized controlled trial of intensive insulin therapy in a surgical ICU suggest that patients with a previous diagnosis of diabetes were at lower risk of mortality than were those without or newly diagnosed with diabetes (odds ratio [OR] 0·356, 95% CI 0·158–0·803, p=0·01). Posthoc analysis of the counterpart to this study in a medical ICU showed a reduction in mortality only in patients

needing an ICU stay of 3 days or longer, and seemingly only in patients with newly discovered hyperglycaemia (11·5% reduction in mortality in patients with new hyperglycaemia *vs* 1·8% increase in mortality with those with known diabetes).[2] In a pooled analysis of both trials, patients with diabetes achieved no survival benefit, although the number of patients with known diabetes was small.[49]

In other randomized studies, results were stratified according to the presence of pre-existing diabetes. Investigators of a small (n=523) single-center study reported no benefit of intensive intravenous insulin therapy with a mean glucose target of 4·4–6·1 mmol/L compared with a target of 10–11·1 mmol/L. This study was powered to detect an 8% absolute risk reduction. No difference in outcomes between patients with or without diabetes was identified. Investigators of a multicenter randomized controlled study of patients with sepsis noted outcomes did not differ between those with or without diabetes treated with intensive insulin therapy. However, this study was stopped before enrolment was completed largely because of frequent hypoglycaemia.[50]

A pivotal, large, multicenter randomized controlled trial (NICE-SUGAR) comparing conventional (<10 mmol/L) versus tight (4·5–6·0 mmol/L) glycemic control using intravenous insulin infusions in ICU patients showed increased mortality for patients in the intensive arm (OR 1·14, 95% CI 1·02–1·28, p=0·02). The treatment effect did not differ between surgical and non-surgical patients, nor was a difference observed between patients with or without known diabetes.[51]

Other non-randomized or observational studies provide less robust data than does the NICE-SUGAR trial but deserve mention because they attempt to identify patients with stress hyperglycemic. In a mixed surgical (n=676), medical (n=1856), and trauma (n=134) ICU, outcomes in patients with diabetes (n=532) were compared with those in patients without known diabetes after implementation of a moderately tight glycemic control protocol (target blood glucose concentrations 6·9 mmol/L). Mortality was significantly reduced in non-diabetic patients but not in those with known diabetes. Furthermore, in patients without diabetes, mortality began to rise when mean glucose concentration exceeded 7·8 mmol/L in patients without diabetes, whereas in patients with diabetes this threshold was 10 mmol/L.[52]

Several observational studies have assessed whether patients with stress hyperglycemia have a high risk of poor outcomes. A large observational study of 728 patients with diabetes and 4218 patients without diabetes established that at any mean ICU glucose concentration, ICU (but not hospital) mortality is greater (up to nearly four times) in patients without diabetes than in those with the disorder, even after adjustment for disease severity (Acute Physiology and Chronic Health Evaluation II score). In a mixed ICU sample of 2826 patients, those without diabetes who needed treatment for hyperglycemia had higher sequential organ failure assessment (SOFA) scores, greater hospital length of stay (8·0 *vs* 6·7 days, p<0·001), and higher mortality rates (10% *vs* 6%, p<0·01) than did patients with known diabetes, despite lower median glucose and adjustment for severity of illness and other covariates. By contrast, patients with the disorder had the same death rate as normoglycemic non-diabetic patients (6% *vs* 5%), despite higher SOFA scores and median glucose values. The high mortality rate in hyperglycemic patients without known diabetes and absence of relation of hyperglycemia to mortality in patients with diabetes was also reported in mixed ICU populations and in those with severe sepsis. However, not all results from ICU studies show a high risk of mortality related to acute hyperglycaemia.[53]

The relation between newly discovered hyperglycemia and mortality in patients presenting with acute myocardial infarction or acute coronary syndrome has been investigated. Unfortunately, most studies rely on glucose concentrations at admission to identify stress hyperglycemia. In a meta-analysis, the pooled unadjusted relative risk (RR) of in-hospital mortality after myocardial infarction in 1856 patients without diabetes who had stress hyperglycemia at admission was 3·9 (95% CI 2·9–5·4) compared with normoglycemic non-

diabetic patients. By comparison, the risk of death in 688 hyper glycemic patients with diabetes was 1·7 (95% CI 1·2–2·4) relative to normoglycemic patient with diabetes.[54]

Other studies support these findings. In more than 160 000 patients admitted with acute myocardial infarction, glucose concentration at admission was associated with a steep rise in 30-day mortality for those without known diabetes: for glucose concentrations of 6·1–7·8 mmol/L on admission, OR 1·17, (95% CI 1·11–1·24); 13·3 mmol/L or more, OR 1·87, (95% CI 1·75– 2·00). However, for patients with established diabetes, mortality rose only at the highest glucose concentration (>13·3 mmol/L OR 1·32, 95% CI 1·17–1·50). Discrepancies between studies might be explained in part by the length of follow-up—the association between diabetes status and mortality strengthened as the length of follow-up increased. With longer follow-up, the association between diabetes and mortality was significant, but the association with stress hyperglycemia became non-significant.

Another study investigated the role of acute and chronic hyperglycemia in 827 patients with diabetes, 324 of whom had at least two HbA_{1c} measurements in the previous 2 years. Glucose concentrations at admission in the third (2·84 mmol/L, 95% CI 1·04–7·76, p=0·04) or fourth (5·03 mmol/L, 95% CI 1·90–13·26, p=0·001) quartiles independently predicted in hospital mortality after acute myocardial infarction. However, mortality did not differ much between quartiles of HbA_{1c}. Results of another study confirmed no association between mortality and HbA_{1c}, thus drawing attention to the potential importance of acute hyperglycemia over chronic hyperglycemia in hospital in patients with acute myocardial infarction.[55]

A retrospective analysis of 433 patients after stroke established that blood glucose concentrations higher than 10 mmol/L at admission (OR=2·1, 95% CI 1·1–4·6, p=0·02), but not diabetes itself, was an independent predictor of dependency 1 year after first-ever stroke. A meta-analysis showed that in patients without diabetes, stress hyperglycemia (definition varied by study) was associated with a high risk of mortality after stroke (pooled RR 3·07, 95% CI 2·50–3·79). However, this was not true for patients with diabetes (pooled RR 1·30, 95% CI 0·49–3·43). In further studies, Glucose concentration on admission was associated with higher mortality rates in patients without a history of diabetes than in those with a history of diabetes both for ischemic stroke and intracranial hemorrhage. This finding was not confirmed in another study.[56]

In a prospective observational analysis of 262 patients with stroke, researchers used a normal fructosamine and to identify those with transient hyperglycemia. HbA_{1c} Patients with transient hyperglycemia had worse stroke severity scores than did those with either known diabetes or normoglycemia. Furthermore, 30-day mortality was higher in patients with transient hyperglycemia than in those with normoglycemia (27·4% *vs* 12·7%, p=0·01), but no significant difference between patients with diabetes (16·2%) and normoglycemia was reported.[57]

The first Leuven study consisted largely of postsurgical patients, two-thirds of whom had cardio thoracic surgery. Because patients with no history of diabetes benefited most from intensive insulin therapy, the same could be true for the subset of post cardiothoracic surgery patients.

However, a prospective study with historical controls showed reductions in mortality, hospital length of stay, and surgical site infections after cardiothoracic surgery in patients with diabetes who received intensive insulin therapy. By contrast with the Leuven study, in the Furnary study patients with transient hyperglycemia were excluded, indicating that patients with diabetes also benefit from glycemic control. This finding seems to be in agreement with another study.[58]

Chronic hyperglycemia in the perioperative setting also seems to be harmful, affecting the rate of postoperative infections and neurological outcomes. A meta-analysis of 34 trials showed that perioperative insulin infusion reduces mortality but increases rates of hypoglycemia. However, researchers calculated that the available mortality data were too few to reliably detect a plausible treatment effect, and that the presence of diabetes did not affect outcomes. Thus, hyperglycemia in patients with or without

diabetes could adversely affect outcomes after surgery.[59]

Stress hyperglycemia is linked to poor outcomes and the association seems to be stronger for patients without diabetes than for those with pre-existing diabetes. However, studies were not prospectively designed to compare patients with stress hyperglycemia and pre-existing diabetes, creating some limitations. Despite data from interventional studies and controlling for severity of illness, residual confounding could be difficult to eliminate. For example, patients with pre-existing diabetes might be more likely to undergo glycemic monitoring and receive insulin treatment or other life-saving drugs in the hospital than would undiagnosed patients.

Additionally, studies lack a consistent or strict definition of stress hyperglycaemia.[60]

Many studies do not have enough comparator groups because they are observational. For example, direct comparisons of glycemic control in non-diabetic patients who have stress hyperglycemia with diabetic patients are often unable to account for the change in glucose from baseline in the latter. Non-diabetic patients with stress hyperglycemia should ideally be compared with those who have been diagnosed and who have deterioration of pre-illness glycemic control to enable assessment of whether outcomes differ. However, results of a few studies show poor outcomes that persist in patients with newly discovered hyperglycemia, after accounting for glycemic control. Despite these limitations, results of controlled studies seem to show that treatment of hyperglycemia in patients improves outcomes, although new data indicate that the quest for strict normoglycemia is harmful.[55]

In a retrospective study, pre-existing hyperglycemia affected the relationship between acute blood glucose levels and mortality, suggesting a significant interaction between chronic and acute glycemic control.

HbA1c levels were shown to be predictive of mortality in a study of diabetic patients with sepsis. This finding was not replicated in a later study conducted in the ICU of *Hospital de Clinicals de Porto Alegre, Porto Alegre* (RS), Brazil.[62]

V. Relationship Between Glycemic Control in the Critically Ill and Mortality

The relationship between mean glycemia during ICU stay and mortality is distinctly different when comparing patients with and without diabetes. A number of observational cohort studies have demonstrated that for patients without diabetes the lowest mortality is seen in patients with mean blood glucose in the 80–110mg/dl range during ICU stay, with a modest increase associated with mean blood glucose 110 –140mg/dl and progressively higher mortality rates observed with mean blood glucose 140–180mg/dl and higher. In contrast, for patients with diabetes, there is a 'blunted', or even absent, relationship between mean blood glucose above 80–110mg/dl and mortality.

The relationship between diabetes status and outcome in patients with sepsis or acute bacteremia was evaluated in a retrospective cohort study of 128 222 patients admitted with sepsis over a 5- year period to 83 Dutch ICU's. Among patients with diabetes, only hypoglycemia in the absence of severe hyperglycemia was independently associated with risk of death. In contrast, for patients without diabetes, hyperglycemia and hypoglycemia were independently associated with increased risk of death, as was their combination. In a cohort of 317 patients with Acinetobacter baumannii complex bacteremia, the lowest mortality among patients without and with diabetes the lowest mortality was seen with mean blood glucose 70–100 mg/dl and 100–140 mg/dl, respectively.

The studies describing the relationship between mean glycemia and mortality also confirmed the strong association of hypoglycemia with death in critically ill patients with and without diabetes; those with mean blood glucose during ICU stay less than 80 mg/dl sustained the highest mortality. Recently published work suggests that the independent association of hypoglycemia with death may even be stronger in patients with diabetes than in those without.[65]

Several observational cohort studies have demonstrated that high glucose variability is independently associated with risk of death in patients without diabetes, in contrast, there was no association between increasing glucose variability and risk of death for patients with insulintreated diabetes.[66] A recently published multicenter observational cohort study included 90 644 septic patients, 5127 with insulin treated diabetes evaluated glucose metrics in the first 24 h of ICU admission. Patients with insulin-treated diabetes had lower adjusted hospital mortality with higher peak blood glucose levels whereas those without diabetes had increased mortality.

VI. DURING CRITICAL ILLNESSES ACUTE HYPERGLYCEMIA IS MORE TOXIC THAN IN DIABETIC PATIENTS

Different theories regarding acute toxicity of hyperglycemia:

Some theories suggest that subtle molecular differences, patients' genetic background and differences between the acute and chronic status of hyperglycemia are interfering factors. Others point out that intracellular glucose overload during critically illnesses is involved in this scenario. [67]*Glucose transporters & intracellular glucotoxicity***:** It is known that glucose itself influences the regulation and expression of its cellular transporters. Downregulation of GLUTs during moderate hyperglycemia in normal cells is a protective mechanism against glucotoxicity.

Enhanced concentration of cytokines, such as TNFα, angiotensin II and endothelin 1, during the stress response stimulate the translocation and upregulation of glucose transport in different cells. Likewise, hypoxia has the same effect on GLUTs. Therefore, upregulated glucose transporters that are working without the influence of insulin cause extra influx of glucose into the cell. This leads to enhanced intercellular glucose levels in different cell types, including endothelial and epithelial cells, as well as immune cells.[69] Hyperglycemia has been associated with enhanced mitochondrial superoxide production.

Mitochondrial dysfunction, with a failure to produce energy for efficient metabolisms, is the major cause of cellular abnormalities and organ dysfunction leading to multiple syndromes among CIPs who die. Mitochondrial dysfunction is also attributed to insulin resistance. As a result of decreased oxidation of mitochondrial fatty acids, intracellular fatty acyl coenzyme A and diacyl glycerol levels are enhanced. Thus, atypical protein kinase C, JNK and IKKβ are activated to block IRS-1 tyrosine phosphorylation causing insulin resistance. 70

VII. MANAGEMENT OF HYPERGLYCEMIA

Glycemic Targets: The literature is fairly consistent in recommendation values for optimal glycemic control however debates arise over how strict the recommended glucose range should be set and whether there is any discernable advantage of adopting tight glycemic control versus having a more conservative approach. Due to variations in hospitalized patients' nutritional status and other factors contributing to their comorbidities, higher than normal glucose targets can be advised for these patients opposed to those who are in outpatient care. Therapy should be initiated in the majority of critically ill and non-critically ill patients who have consistent levels of hyperglycemia once they have crossed a threshold of >180 mg/dL (10.0 mmol/L) and maintained in a target glucose range of 140-180 mg/dL (7.8-10.0 mmol/L).71 These glucose ranges are maneuverable however and are not a set standard for all hospitalized patients. Certain patients may be given more aggressive goals of < 140 mg/dL (7.8 mmol/L) though glucose levels must be monitored appropriately to prevent hypoglycemia. On the other hand, if patients are in a position where strict glucose monitoring is simply not possible or glucose control is perhaps second to other more significant issues in their medical care such as palliation or severe comorbidities, then a higher target glucose range may be explored. Because of these outliers, an individualized approach to target glucose values may be worth the extra effort as treatment can be tailored to each individual patient to decrease hyperglycemia risk and avoid hypoglycemia due to overaggressive therapy.72

Management of Hyperglycemia in Non-Critically Ill Inpatients: The use of insulin has

become the mainstay of hyperglycemia in the hospital setting. The traditional use of sliding scale insulin was once considered an essential treatment method of high blood glucose levels but has now been considered inappropriate for safe management in hospitalized patients due to the risk of inadequately treated hyperglycemia and severe hypoglycemia. In general medicine and surgery patients who are not in critical care, subcutaneous short-acting insulin before meals or every 4-6 hours if NPO, has become the mainstay of treatment to adequately control hyperglycemia in diabetics and non-diabetics. The basal bolus (prandial) insulin regimen is effective because it follows the physiological response by covering the basal, nutritional and supplemental requirements of insulin production. A study by Korytkowski et al. found increased baseline glucose levels, greater insulin requirements, increased adverse outcomes, and a greater incidence of hypoglycemia in patients treated with sliding-scale regular insulin versus a basal dose of insulin glargine with SSRI. In patients being treated solely with SSRI therapy, they had a three times greater chance of having blood glucose levels >300mg/dL compared to those given basal-bolus insulin. A prospective randomized multicenter trial found 14% of patients being treated with sliding-scale insulin therapy had a blood glucose >240mg/dL despite administering higher insulin doses compared to patients treated with insulin glargine and glulisine, though no differences in length of hospital stay or incidence of hypoglycemia were noted.[73] A sliding - scale regimen can be of use for initial therapy in non-diabetic patients with moderate hyperglycemia, however these patients should be transitioned to a scheduled insulin regimen once insulin requirement is determined. The issue with treating patients with SSRI therapy is that the underlying mechanism acts to correct hyperglycemia only when it occurs and has no beneficial effect of preventing or decreasing recurrences of hyperglycemia, something which a basal-bolus regimen can achieve.[74]

The use of a constant intravenous insulin infusion has the benefit of a very rapid achievement of glycemic control however it is not recommended in non-critical care patients in many hospitals, especially when feeding protocols are subject to change, requiring insulin dosage to be adjusted accordingly. If patients are being weaned off of intravenous insulin during their hospital care, a proper transition protocol to subcutaneous insulin can lower costs and prevent morbidity and is thus recommended. Consideration about the patient's age, comorbidities, renal function, and nutritional intake should all influence the clinician's decision about the amount of total daily insulin required for patients. Most patients should be started with a starting total daily dose of insulin between 0.3 and 0.5 units/kg as higher doses greater than 0.6 to 0.8 units/kg/day have been associated with hypoglycemia. The seemingly increased safety profile of basal bolus (prandial) insulin regimen as well as its success rate of achieving and maintaining appropriate glucose levels in treated patients should lead to its uniform implementation in hospitalized non-critical care patients.[75]

Noninsulin antihyperglycemic treatments are currently not recommended in the treatment of hospitalized patients as evidence regarding safety and efficacy is lacking. Many inpatients in the hospital have clear contraindications for the use of certain oral antihyperglycemic agents.

Metformin is generally not prescribed for patients with renal insufficiency, hepatic and cardio-vascular disease due to concerns over lactic acidosis though its use in the hospital is still common despite these concerns. Sulfonylureas act as long-acting insulin secretagogues and are very commonly used in patients with type 2 diabetes however their side effect profile includes a high risk of hypoglycemia, limiting its use for inpatients. A nested case-control study showed 19% of hospitalized patients taking a sulfonylurea developed hypoglycemia, with the majority of cases occurring in patients older than 65 years, those with decreased GFR of 30ml/minute /1.73m2 and those who were receiving concurrent intermediate or long-acting insulin while being treated with a sulfonylurea. Patients being treated with a sulfonylurea have the increased risk of prolonged hypoglycemia due to the pharma-codynamics of the agent, and require further monitoring and strict management with glucose preparations. Other oral antihyperglycemic

agents such as thiazolidines, Sodium glucose co - transporter 2 inhibitors, α - glucosidase inhibitors and incretin based therapies generally have side effect profiles and contraindications in hospitalized patients that substantially limit their use for inpatient treatment.[76]

Management of Hyperglycemia in Critically Ill Inpatients: Insulin is indisputably the gold standard for treating critically ill patients in the hospital setting, as agreed upon by most of the literature. Intravenously administered insulin is preferred due to its rapid delivery which allows for quick correction of deteriorating glucose levels with greater predictability and effectiveness compared to subcutaneously administered insulin. However, infusing insulin intravenously is quite labor intensive and in a majority of health centers requires ICU admission for proper administration and monitoring. In the critical care setting, predetermined written or computer protocols factoring glycemic fluctuations and insulin dose may be used for adjustments of the infusion rate when considering infusing patients with insulin. Obvious fluctuations in the patients' clinical status and glucose targets should be accounted for when adjusting insulin infusion rates. Traditionally a blood glucose target was achieved by using a drip which was mathematically calculated by the medical staff using an established algorithm. Unfortunately, errors in dosing can be common due to human errors which is why computer protocols have set the stage to replace simple predicting on the physicians part. Computer based algorithms proved to deliver tighter glycemic control with less risk of hypoglycemia when compared to the traditional paper protocol.[77]

VIII. HYPERGLYCEMIA IN HIGH RISK PATIENTS

Certain subsets of patients are deemed high risk due to their underlying comorbidities, concurrent medications and procedures in the hospital which can contribute to hyperglycemia. Corticosteroids, which are commonly used in the hospital as a single therapy or in combination therapies, can contribute to hyperglycemia more commonly by late morning when it is prescribed, but can have a prolonged effect throughout the course of the day if daily doses are required. It is essential to monitor capillary blood glucose values in patients on high dose corticosteroids, especially during the period 4 to 8 hours after oral administration and sooner after intravenous administration. A basal dose of intermediate or long acting insulin may be able to offset the increased glucose levels of early morning corticosteroid therapy, however care should be taken to avoid episodes of hypoglycemia when long acting insulin preparations are used in these cases. The COIITSS study hypothesized that patients being treated for septic shock in the ICU with corticosteroids may benefit with intensive insulin therapy versus a conservative therapy, even though general ICU patients may not. Prolonged bed rest for as little as seven days in hospitalized patients may also contribute to insulin resistance in skeletal muscle and decreased glucose uptake. Severe hyperglycemia (minimum 9.99 mmol/L) has been shown to increase the likelihood of developing graft versus host disease in nondiabetic patients after allogenic stem - cell transplantation, though the researchers' results were found in non-obese patients only.[81] One study analyzing cardiac surgery patients found that while glucose concentrations were lower at the end of surgery with intensive insulin treatment, there was no decrease in perioperative death and mortality between this group and the conventional treatment group, in fact showing more deaths and strokes in the intensively treated group. Intensive glycemic control in the range of 80- 180 mg/dL (4.4-10 mmol/L) was not shown to benefit perioperative patients with diabetes undergoing surgical procedures and showed a higher incidence of hypoglycemia in these patients, advising against practicing tight glycemic control in surgical patients. A multicenter randomized trial found improved glycemic control in general surgery patients with a basal plus regimen with glargine once daily and corrective glulisine before meals compared to a standard basal-bolus regimen.[82]

IX. TARGET OF GLUCOSE CONTROL IN CRITICALLY-ILL PATIENTS

In the clinical studies on intensive insulin therapy, it is impossible to completely distinguish

the impact of insulin infusion from that of blood glucose control as both are done concomitantly.

Therefore, a four-arm design study was set up in a rabbit model of prolonged critical illness. Two norm insulinemic and two hyperinsulinemia groups were each controlled to either normal or elevated glucose levels. The study revealed that glycemic control mediated the survival benefit of intensive insulin therapy, independent of insulin.

Indeed, mortality was 41.4% in hyperglycemic versus 11.1% in normoglycemic rabbits, whereas insulin levels did not contribute to the survival benefit.[85] The clinical data are in agreement with this experimental observation. In the Leuven surgical study, the risk of death appeared to be linearly correlated with the degree of hyperglycemia, with no clear cut-off level below which there was no further benefit.

Conventionally treated patients who developed severe hyperglycemia (150–200 mg/dl) carried the highest risk of death, this risk was intermediate for patients who received conventional insulin therapy and who developed only moderate hyperglycemia (110–150 mg/dl), whereas the lowest risk was present in the patients whose blood glucose levels were controlled to strict normoglycemia below 110 mg/dl with intensive insulin therapy. This relation of risk of death with strata of glucose control was confirmed in the mixed medical/surgical patient population, with most benefit gained when glycemia was controlled below 110 mg/dl. Patients with diabetes appeared to behave differently though, with an inverse pattern for the 3 strata of glucose control, although no significant differences were noted among these 3 levels.[86,87]

Glycemic control also accounted for most effects of intensive insulin therapy on morbidity of critical illness. Tight glycemic control below 110 mg/dl appeared to be of crucial importance for the prevention of bacteremia, anemia, and acute renal failure[86,87] and for reducing the risk of critical illness polyneuropathy, for which a positive linear correlation was observed with glycemia.[88] The superior clinical benefit with glucose control below 110 mg/dl underscores the importance of achieving the normoglycemic target range. Seventy percent of the patients allocated to intensive insulin therapy in the Leuven studies achieved a mean daily blood glucose level below 110 mg/dl. At the time of interim analysis of the GLUCONTROL study, median (interquartile range) levels of glucose were 147 (127–163) mg/dl in the conventional and 118 (109–131) mg/dl in the intensive insulin group (Preiser JC, data presented at the 19th European Symposium on Intensive Care Medicine, Barcelona, Spain, September 2006).

This means that tight glycemic control was achieved in only approximately 25% of the patients on intensive insulin therapy.[89,90]

Communication and Discharge of Hyperglycemic Patients: Generally, a patient with an HbA1C of less than 6.5% can be discharged with no antidiabetic treatment, and those with elevated HbA1C levels should be prescribed insulin, oral antihyperglycemic agents or combination therapies for the outpatient setting. Proper communication is imperative to ensure the patient administers their treatment correctly and at the appropriate times in order to prevent aberrations in their glucose levels. Due to the complexity of insulin treatment regimens, it is recommended that written orders be given to the patient as oral communication can lead to errors and complications in management. To prevent these types of errors, several organizations have implemented strategies that incorporate clear, formal discharge instructions about medications and follow up appointments, however evidence is still lacking regarding the ideal method of providing a safe transition to the outpatient setting. A systematic review found that patients who have been treated for stress hyperglycemia in the hospital are at increased risk for developing subsequent diabetes and should be followed up accordingly. Another study determined a prevalence of new-onset diabetes of 8% in stress hyperglycemia patients during follow up and noted a positive correlation between the degree of in-hospital hyperglycemia and risk of subsequent diabetes development. Hospitalized in patients with severe hyperglycemia showed a striking 28% increased risk of developed new-onset diabetes after discharge. This perceived link necessitates

further research into the development of new-onset diabetes in stress-hyperglycemia patients and reiterates the importance of proper discharge orders and follow up appointments in such patients as research on the pathophysiology of such events is still lacking.[98]

Objective:

- To determine mean hospital, stay in critically ill patients admitted in hospital.
- To compare mean hospital, stay mong critically ill patients with hyperglycemic versus normoglycemic.

X. PATIENTS AND METHODS

This descriptive study of 7 months was conducted in the setting of Department of Internal Medicine, The Aga Khan University Hospital.The sample size for this study is 151 patients as calculated by using WHO sample size calculator. Mean length hospital stay = 5.4±1.0 (12), margin of error = 0.16. Nonprobability consecutive sampling was done Patients' age varied between 18- 75 years, blood sugar of >140mg/dl on admission to SCU/ICU was marked as cases and blood sugar of <140mg/dl on admission to SCU/ICU was labelled as control. Those with known diabetes or taking medications causing hyperglycemia (Steroids) were excluded from the study.

Patients fulfilling the mentioned-above inclusion criteria were included in the study. Mean hospital stay was seen in critically ill patients and comparison between hyperglycemic versus normoglycemic were done among those patients. Detailed patient demographics e.g. Age, gender, HBA1c levels were recorded. The first blood glucose level from a peripheral blood draw on the day of admission was used as the admission blood glucose value. Data was also recorded for reasons for admissions e.g. HTN, CKD, Stroke, IHD, sepsis and MI. Hospital stay was measured in all patients. All the gathered information was a pre-designed Proforma. All the collected data was entered and analyzed by using the SPSS (version-23). Variables were recorded include continuous variables such as age, blood sugar levels, length of hospital stay were reported as mean ± standard deviation. Frequency and percentage were calculated gender, reasons of hospital admission e.g. HTN. CKD, STROKE, IHD, sepsis and MI. stratification of effect modifiers e.g. age, gender, reasons of hospital admission was done. Post-stratification independent sample t-test was applied. P-value of <0.005 was taken as statistically significant difference. Comparison of mean hospital stay between hyperglycemic versus normoglycemic was done using independent sample t-test.

XI. RESULT

Mean age of patients included in this study was 55.40±17.20 years. Minimum age was 20 years and maximum age was 75 years.

Mean hospital stay was 6.45±5.82 days. Minimum hospital stay was 01 day and maximum stay was 35 days (Table 1).

Table 1

Hospital stay (Days)	
Mean	6.45
S.D.	5.82
Minimum	01
Maximum	35

Mean blood sugar level was 179.36±69.21 mg/dl. Minimum blood sugar level was 60.00 mg/dl and maximum stay was 560.00 mg/dl (Table 2).

There were more males as compared to females. There were 79 (52.32%) male and 72 (47.68%) female patients (Figure 1).

Table 2

Blood Sugar level (mg/dl)	
Mean	179.36
S.D.	69.21
Minimum	60.00
Maximum	560.00

On frequency of reason for admission, 19 (12.58%) patients were having MI/heart failure, 01 (0.68%) road traffic accidents, 13 (8.61%) acute kidney injury, 83 (54.97%) sepsis/ infections, 2 (1.32%) hypertensive emergency, 15 (9.93%) stroke and 18 (11.92%) patients were having COPD/Asthma/interstitial lung disease (ILD) (Figure 2).

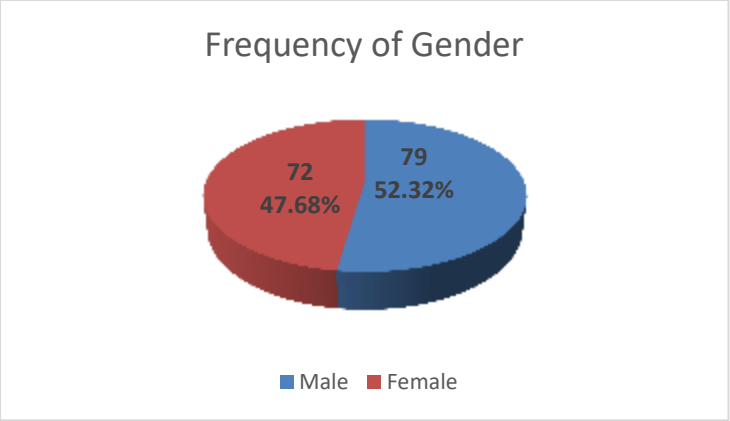

Figure 1

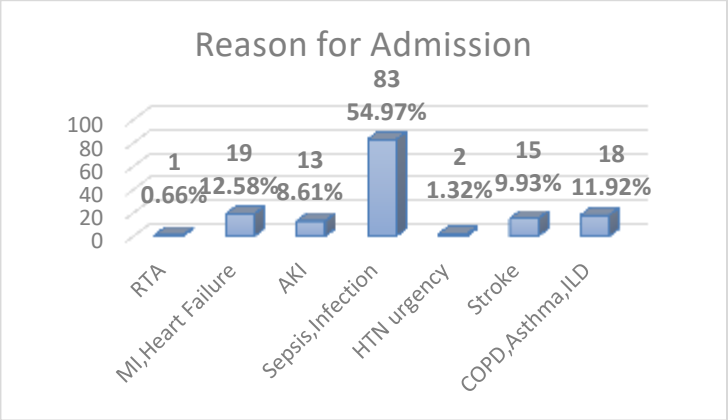

Figure 2

Hyperglycemia was diagnosed in 134 (88.74%) patients.

On comparison of mean hospital stay between the groups, mean hospital stay in hyperglycemia group was 6.70±6.09 days versus 4.52±2.03 days in normoglycemia group. This difference was statistically insignificant with p-value of 0.004.

Stratification of age was performed, in age group of 18-50 years, mean hospital stay in hyperglycemia group was 8.06±7.50 days and 5.14± 2.54 days in normoglycemia group. This difference was statistically significant with p-value of 0.05. In age group of 51-75 years, mean hospital stay in hyperglycemia group was 5.97 ±4.10 days and 5.08±1.59 days in normoglycemia group. This difference was also statistically significant with p-value of 0.01 (Table 4).

Table 4: Stratification of age to determine the association of age with mean hospital stay between the groups

Age Group	Hospital Stay	Groups		P- value
		Hyperglycemia	Normoglycemia	
18-50 Years	Mean	8.06	5.14	0.05
	S.D.	7.50	2.54	
51-75 Years	Mean	5.97	5.08	0.01

Table 5: Stratification of gender to determine the association of gender with mean hospital stay between the groups

Gender	Hospital Stay	Groups		P- value
		Hyperglycemia	Normoglycemia	
Male	Mean	6.21	4.40	0.04
	S.D.	5.63	1.83	
Female	Mean	7.23	4.71	0.05
	S.D.	6.55	2.42	

Stratification of gender was also performed, in males, mean hospital stay in hyperglycemia group was 6.21±5.63 days and 4.40±1.83 days in normoglycemia group. This difference was statistically significant with p-value of 0.04. In females, mean hospital stay in hyperglycemia group was 7.23±6.55 days versus 4.71±2.42 days in normoglycemia group. This difference was also statistically significant with p-value of 0.05 (Table 5).

Stratification was also performed on the basis of reason for admission. There is no significant association was found of its with hospital stay between the groups.

XII. DISCUSSION

Hyperglycemia is a condition frequently encountered in daily practice with hospitalized patients. It is estimated that nearly 25–35 % of admitted patients are hyperglycemic. [99] Several studies have shown that hyperglycemia is associated with poor outcomes and extended hospital stay in patients hospitalized for various conditions and in different settings (i.e. coronary care and intensive care units, post-operatively).[100-102]. In present study, we determined the association of hyperglycemia with hospital stay in critically ill non-diabetic patients. In our study, hospital stay was significantly higher in patients with hyperglycemia. Lipton reported that patients admitted to the intensive cardiac care unit had a longer length of stay and increased mortality if they were in the upper tertile of admission glucose levels.[103] In addition, these investigators noted that hypoglycemia was associated with an increased mortality rate and that an increase in the average glucose level during the ICU stay was associated with increased mortality. Williams et al. have reported that stroke patients complicated with hyperglycemia had longer hospital stay (7 vs. 6 d, p-value 0.015) and higher inpatient hospital charges ($6611 vs. $5262; p < 0.001).104 Karetnikova et al. studied 529 patients admitted with an ST-segment elevation myocardial infarction. They found a linear association between the blood glucose level and in-hospital mortality in nondiabetic patients.[105] Kasirye et al. studied 209 patients admitted to the hospital with an acute exacerbation of COPD. They did not find any correlation between hyperglycemia and adverse outcomes, including increased length of stay, 30-day readmission rates, and 90-day all-cause mortality.[106]

Van Vught did an extensive study of the relationship between the admission glucose levels and outcomes in critically ill patients with sepsis. This study included 987 patients, including 201 patients with severe hyperglycemia defined by glucose levels greater than 200 mg/dL. Multivariable regression analysis demonstrated that patients with severe hyperglycemia had an increased risk of mortality by day 30. This occurred in patients both with diabetes and without diabetes. This association between severe hyperglycemia and mortality persisted in patients after adjustment for lactic levels in patients with diabetes but not in patients without diabetes.[107]

Sung and colleagues prospectively collected data on 1,003 consecutive trauma patients admitted to an intensive care unit over 2 years. Twenty-five percent of these patients had severe hyperglycemia defined by glucose levels>200 mg/dl. These patients with severe hyperglycemia

had an increased risk of infection, longer hospital lengths of stay, and higher mortality after adjustment for age and the injury severity score. These five studies demonstrate that admission levels of glucose have important associations with outcomes in patients presenting to emergency departments, in patients admitted to intensive care units, and in patients admitted with trauma.[108]

In summary, hyperglycemia is a frequent condition occurring in critically ill patients. Patients with stress hyperglycemia have a longer average hospital stay, although it remains unresolved whether stress hyperglycemia is a determinant rather than a marker of increased morbidity and mortality in critically ill patients. Furthermore, identifying previously unknown diabetes has relevant therapeutic implications and represents a great opportunity for prevention of diabetes related acute and chronic complications.

XIII. CONCLUSION

Our study showed a positive association between hyperglycemia and length of stay in critically ill patients. Therefore, hyperglycemia can be used as a predictor of increased hospital stay in critically ill non-diabetic patients.

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