REVIEW ARTICLE

STRESS HYPERGLYCEMIA

*Dr. Balram Sharma

Associate Professor (Endocrinology), SMS Medical College, Jaipur (Raj)

ARTICLE INFO	ABSTRACT
	Stress hyperglycemia is a heterogeneous entity with unique pathophysiological features. Present practice is to treat hyperglycemia irrespective of its cause. The optimum target glucose range in stress conditions is still undefined, and different targets should be compared on the basis of their risk-to-benefit ratios and individualized decision should be taken. Still large prospective studies with follow-up data comparing diabetes and stress hyperglycemia are needed.

INTRODUCTION

Stress hyperglycemia is common in critically ill patients and appears to be a marker of disease severity, poor clinical outcomes, including mortality, morbidity, length of stay, infections and overall complications. (Badawi *et al*., 2012; Bruno *et al*., 2002; Capes *et al*., 2000; Dungan *et al*., 2009) The metabolic response to stress increases flux of energy substrates to tissues that need it. Brain is the major user of glucose in the fasting state and its rate of utilization is independent to insulin and hence maintenance of central glucose delivery depends solely on the plasma glucose concentration and adequate cerebral blood flow. Thus, stress hyperglycemia serves as a means of ensuring adequate delivery of glucose to the brain during stress. Glucose uptake into the central nervous system (CNS) is sufficient above 70 mg/dL of plasma glucose levels. While fasting, the brain can reduce its obligatory need for carbohydrate by approximately 50% without interfering with neuronal function. However, further reduction of blood glucose leads to compromised glucose uptake by brain and eventually results in compromised brain function and neuronal death. Thus, during a prolonged fast stress hyperglycemia is needed to compensate for any compromise of cerebral blood flow causing a reduced rate of glucose delivery to the brain. (Havel and Taborsky, 2003)

Pathophysiology

Regulation by the Central Nervous System: Afferent inputs to the CNS such as oxygen and pH chemoreceptors in the carotid bodies, pressure sensors in the carotid sinus and the aortic arch, and glucose receptors in the liver and the brain can signal the need for increased carbohydrate flux to the brain. These signals are integrated in higher centers of brain and initiate efferent responses that influence carbohydrate metabolism and thus lead to stress hyperglycemia by stimulating hepatic glucose production, impairing peripheral glucose utilization and impairing the islet responsiveness to glucose.
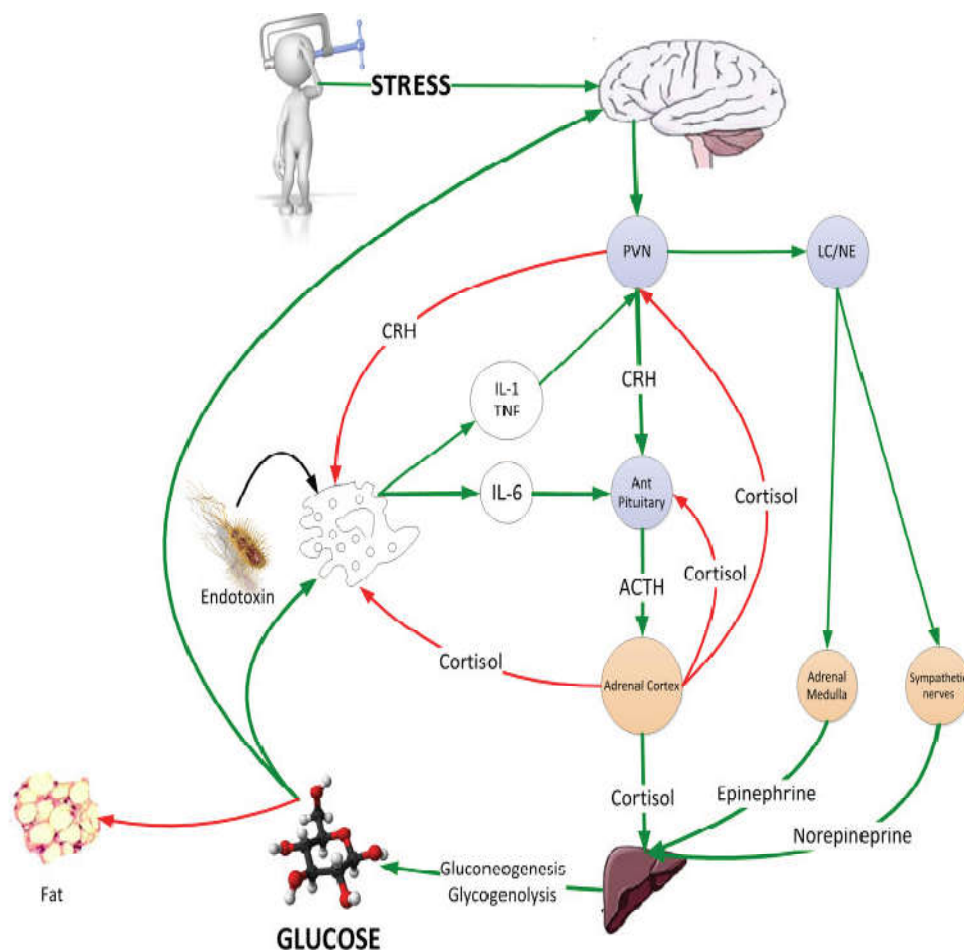
Neuroendocrine Signals (Figure 1)

Increased secretion of epinephrine, norepinephrine, cortisol, growth hormone (GH) and glucagon, and decreased secretion of insulin happens during stress. These changes produce hyperglycemia by altering regulation of plasma glucose. (Havel and Taborsky, 2003) ACTH, adrenocorticotrophic hormone; CRH, corticotrophin releasing hormone; LC/NE, locus ceruleus norepinephrine system; PVN, paraventricular nucleus.

Diagnosis

Stress hyperglycaemia can be labelled as transienthyperglycaemia during illness and is usually restricted topatients without previous evidence of diabetes. However, the identification of such patients is complex as many type 2 DM patients are diagnosed in hospital with stress hyperglycemia. No guidelines specifically define stress hyperglycaemia. According to American Diabetes Association (ADA), patients of stress hyperglycemia can be classified into one of three groups—known diabetes, newly diagnosed diabetes, and hospital-relatedhyperglycaemia. (Clement *et al*., 2004)

Corresponding author: **Dr. Balram Sharma,**
Associate Professor (Endocrinology), SMS Medical College, Jaipur (Raj)

Figure 1. The neuroendocrine response to stress is characterized by gluconeogenesis and glycogenolysis resulting in stress hyperglycemia providing the immune system and brain with a ready source of fuel. (Stress hyperglycemia, 2013)

However, this classification needs information regarding previous medical history of patient that is usually not available in hospital settings. Change in glucose from baseline rather than the absolute glucose concentration is more important, irrespective of whether a patient has pre-existing diabetes.

Classification of hyperglycaemia in hospital (Kitabchi *et al.*, 2008)

Known diabetes: Diabetes diagnosed and treated before admission

Newly diagnosed diabetes: Fasting glucose more than 6·9 mmol/L or random glucose higher than 11·1 mmol/L during hospital stay and confirmed after discharge

Hospital-related hyperglycaemia: Fasting glucose more than 6·9 mmol/L or random glucose higher than 11·1 mmol/L during hospital stay that reverts to normal range after discharge.

Management

Current guidelines do not recognise stress hyperglycaemia different from pre-existing diabetes. Guidelines exist to specify separate targets for ICU and non-ICU patients. Insufficient data is available to recommend risk stratification for assignment of glucose targets with respect to the cause or severity of hyperglycaemia. It has been noted that rapid correction of underlying pathohysiology is detrimental. (Van den Berghe *et al.*, 2006) It is recommended that less intensive target (mean

glucose 8 mmol/L) should be implemented. (American Diabetes Association, 2009; The Endocrine Society, 2009) Outside of the ICU, individualised glucose targets based on outpatient recommendations should be implemented. (AACE Diabetes Mellitus Clinical Practice Guidelines Task Force, 2007; American Diabetes Association, 2009) Stress hyperglycaemia by definition is a transient, dynamic disorder that responds to changes in disease course. Specific recommendations for treatment of stress hyperglycaemia include insulin therapy which is rapidly titratable in response to changes in glucose concentrations. Intravenous insulin is highly effective and can be adjusted frequently. Subcutaneous insulin is not preferred because it may result in insulin stacking and hypoglycaemia in patients with oedema or hypoperfusion. (Ariza-Andraca *et al*., 1991) Intravenous insulin infusion has concerns about safety and adequate staffing in many ICU settings. In most general surgical and medical patients outside the ICU, subcutaneous insulin can be considered. Insulin analogues usually produce a lower incidence of hypoglycaemia than do regular human insulin or neutral protamine hagedom (NPH) insulin In the outpatient setting. (Umpierrez *et al*., 2009) According to the results of randomised controlled trial of insulin naive patients with diabetes showed that subcutaneous basal bolus insulin was better than was sliding-scale insulin for attainment of safe, effective glycaemic control. (Umpierrez *et al*., 2007) Therapy should be adjusted in response to changes in nutritional needs such as inclusion of consistent carbohydrate diets or injecting prandial insulin according to estimated carbohydrate intake. The amount of exogenous, intravenous, and enteral glucose given can be restricted when necessary by

changing enteral formulas. Fluctuations in glucose might be kept to a minimum with physiological insulin replacement, to ensure adequate carbohydrate coverage. (Kudva *et al.*, 2007; Saudek *et al.*, 1996) Additional subcutaneous short-acting insulin along with insulin dripmaybe necessary to prevent rapid glucose excursions in patients with intermittent exogenous carbohydrate exposure. (Davidson *et al.*, 2005) Use of oral hypoglycaemic agents is usually not recommended for hospital inpatients because of the unpredictable and often slow onset of action, risk of hypoglycaemia in patients with unpredictable nutritionalintake, and presence of contraindications, such as administration of contrast dye in patients taking metformin. (Krinsley and Grover, 2007)

In-Hospital Glycemic Control Targets: Recommendations (Vancheri *et al.*, 2005)

In 2009, the AACE and the American Diabetic Association put forward their recommendations of in-patient glycemic control:

- A target of 140–180 mg/dL (7.8–10.0 mmol/L) is preferable in most patients
- A target of 110–140 mg/dL (6.1–7.8 mmol/L) may be appropriate in selected patients

Merits of Intravenous Insulin Therapy

The mechanisms behind the improved outcomes from intravenous insulin can be due to itsvasodilatory, anti-inflammatory and antiatherogenic effects. Insulin has shown to induce a dose-dependent increase in nitrous oxide synthase production in the endothelium in in-vitro studies. This shows that insulin treatment may improve endothelial function in patients with diabetes.

Conclusion

For plasma glucose regulation, neural regulation of pancreatic islet in conjunction with other hormonal glucoregulatory systems is important. This contributes significantly to the normal disposition of exogenous nutrients and to the glycemic response to environmental stress. The neuroendocrine system modulates the intrinsic regulatory control system for plasma glucose. This involves the liver, peripheral tissues and islet as the primary nutrient and substrate sensors. The function of all the three elements of this system is torespond to neuroendocrine control. Stress responses may or may not be beneficial for long-term survival. Thus, evaluation of the impact of the hyperglycemia should be considered for treatment. Treatment considerations vary in different patients depending upon the nature of the stress and the specific response to that stress in the individual case. Type 2 DM frequently presents for the first time at hospitalization for acute illness, which gets complicated by stress hyperglycemia resulting from the catecholamine and cortisol elevation. Neuroendocrine abnormalities are common in DM. Many a times, a pathophysiologic separation of stress hyperglycemia and Type 2 diabetes is not possible as both involve alterations of the regulation of hepatic glucose output, peripheral sensitivity of tissues to insulin and alterations of islet function. Therefore, neuroendocrine control systems must be taken into account in the diagnosis, evaluation and treatment of any hyperglycemic state in humansn, regardless of etiologic significance. (Havel and Taborsky, 2003)

REFERENCES

AACE Diabetes Mellitus Clinical Practice Guidelines Task Force. American Association of Clinical Endocrinologists medicalguidelines for clinical practice for the management of diabetes mellitus. *EndocrPract.*, 2007; 13 (suppl): 1–68.

American Diabetes Association. Joint statement from ADA andAACE on the NICE-SUGAR study on intensive versus conventionalglucose control in critically ill patients. http://www.diabetes.org/formedia/pr-NICE_SUGAR-study.jsp (accessed May 1, 2009).

American Diabetes Association. Standards of medical care indiabetes–2009. Diabetes Care 2009; 32 (suppl 1): 13–61.

Ariza-Andraca CR, Altamirano-Bustamante E, Frati-Munari AC, Altamirano-Bustamante P, Graef-Sanchez A. 1991. Delayed insulinabsorption due to subcutaneous edema. *Arch Invest Med.*, 22: 229–33.

Badawi O, Waite MD, Fuhrman SA, Zuckerman IH. 2012. Association betweenintensive care unit-acquired dysglycemia and in-hospital mortality. *Crit Care Med.*, 40:3180-3188.

Bruno A, Levine SR, Frankel MR, Brott TG, Lin Y, Tilley BC, Lyden PD, BroderickJP, Kwiatkowski TG, Fineberg SE. 2002. Admission glucose level and clinicaloutcomes in the NINDS rt-PA Stroke Trial. *Neurology*, 59:669-674.

Capes SE, Hunt D, Malmberg K, Gerstein HC. 2000. Stress hyperglycaemia andincreased risk of death after myocardial infarction in patients with andwithout diabetes: a systematic overview. *Lancet*, 355:773-778.

Clement S, Braithwaite SS, Magee MF, *et al.* 2004. Management of diabetesand hyperglycemia in hospitals. *Diabetes Care*, 27: 553–91.

Davidson PC, Steed RD, Bode BW. 2005. Glucommander:a computer-directed intravenous insulin system shown to be safe, simple, and effective in 120 618 h of operation. *Diabetes Care*, 28: 2418–23.

Dungan K, Braithwaite SS, Preiser JC. 2009. Stress hyperglycemia. *Lancet*, 373:1798-1807.

Havel PJ. and Taborsky GJ. 2003. Stress-induced activation of the neuroendocrinesystem and its effects on carbohydrate metabolism. In: Porte D, SherwinRS, Baron A (Eds). Ellenberg& Rifkin's Diabetes Mellitus, 6th edn. NewYork: McGraw-Hill; pp. 127-49.

Kitabchi AE, Freire AX, Umpierrez GE. 2008. Evidence for strict inpatientblood glucose control: time to revise glycemic goals in hospitalizedpatients. *Metabolism*, 57: 116–20.

Krinsley JS. and Grover A. 2007. Severe hypoglycemia in critically ill patients:risk factors and outcomes. *Crit Care Med.*, 35: 2262–67.

Kudva YC, Basu A, Jenkins GD, *et al.* 2007. Glycemic variation andhypoglycemia in patients with well-controlled type 1 diabetes on amultiple daily insulin injection program with use of glargine andultralente as basal insulin. *EndocrPract*, 13: 244–50.

Saudek CD, Duckworth WC, Giobbie-Hurder A, *et al.* 1996. For the Department of Veterans Aff airs Implantable Insulin Pump Study Group. Implantable insulin pump vs multiple-dose insulin fornon-insulin-dependent diabetes mellitus: a randomized clinicaltrial. *JAMA*, 276: 1322–27.

Stress hyperglycemia: an essential survival response! Paul E Marik and RinaldoBellomoMarik and BellomoCritical Care 2013, 17:305 http://ccforum.com/content/17/2/305.

The Endocrine Society. Endocrine Society statement to providers on NICE-SUGAR. http://www.endo-society.org/

advocacy/legislative/SocietyStatementtoProvidersonNICE-SUGAR.cfm# (accessed May1, 2009).

Umpierrez GE, Hor T, Smiley D, *et al*. 2009. Comparison of inpatientinsulin regimens with detemir plus aspart versus neutral protaminehagedorn plus regular in medical Patients with Type 2 Diabetes. *J ClinEndocrinolMetab*., 94: 564–69.

Umpierrez GE, Smiley D, Zisman A, *et al*. 2007. Randomized study ofbasal-bolus insulin therapy in the inpatient management of patientswith type 2 diabetes (RABBIT 2 Trial). *Diabetes Care*, 30: 2181–86.

Van den Berghe G, Wilmer A, Milants I, *et al*. 2006. Intensive insulin therapy in mixed medical/surgical intensive care units: benefit versus harm. *Diabetes*, 55: 3151–59.

Vancheri F, Curcio M, Burgio A, *et al*. 2005. Impaired glucose metabolismin patients with acute stroke and no previous diagnosis of diabetesmellitus. *QJM*, 98: 871–78.

****