Chapter 38
Stress Hyperglycemia

Anand Moses

INTRODUCTION
The main role of the metabolic response to stress is to increase flux of substrates to tissues that need it. The brain is the major user of glucose in the fasting state and its rate of utilization is not dependent on insulin. Therefore, maintenance of central glucose delivery depends solely on the plasma glucose concentration and adequate cerebral blood flow. Thus, stress hyperglycemia can be viewed as a means of ensuring adequate delivery of glucose to the brain during stress. During conditions where there is normal cerebral blood flow, glucose uptake into the central nervous system (CNS) is sufficient if plasma glucose levels are above 70 mg/dL. Increased production of ketone bodies from the liver during a prolonged fast and their utilization by the brain can reduce its obligatory need for carbohydrate by approximately 50% without interfering with neuronal function. Any further reduction of brain, glucose uptake compromises of brain function and eventually results in neuronal death. Thus, even during a prolonged fast, any compromise of cerebral blood flow leads to the need for stress hyperglycemia to compensate for a reduced rate of glucose delivery to the brain.1

MECHANISM
Regulation by the Central Nervous System
Stress hyperglycemia is regulated by central mechanisms. Afferent inputs to the CNS can signal the need for increased carbohydrate flux to the brain. These include oxygen and pH chemoreceptors in the carotid bodies, pressure sensors in the carotid sinus and the aortic arch, temperature receptors and pain receptors in the skin, and glucose receptors in the liver and the brain. Such signals are integrated in higher centers including the hypothalamus which plays an important role in integrating the autonomic efferent responses that influence carbohydrate metabolism and thus lead to stress hyperglycemia. These responses stimulate hepatic glucose production, impair peripheral glucose utilization and impair the islet responsiveness to glucose. The adipose tissue hormone leptin also appears to play a role in causing stress hyperglycemia.

Neuroendocrine Signals
Components of neuroendocrine activation during stress include increased secretion of epinephrine, norepinephrine, cortisol, growth hormone (GH) and glucagon, and decreased secretion of insulin. These changes produce hyperglycemia by interfering with all of the main mechanisms responsible for the regulation of plasma glucose. This neuroendocrine pattern can be reproduced by stimulation of the ventromedial hypothalamus.1

CLINICAL FORMS OF STRESS-INDUCED HYPERGLYCEMIA
- Hypoxia
- Hypotension
- Hypoglycemia—by causing neuroglucopenia
- Myocardial infarction (MI)
- Surgery
- Burns
- Trauma
- Cold stress.

STRESS-INDUCED HYPERGLYCEMIA IN DIABETES MELLITUS
Potential Role in the Etiology of Type 1 Diabetes Mellitus
Injury and destruction of the islets precede the onset of clinical hyperglycemia in Type 1 diabetes mellitus (DM). This represents the activation of an autoimmune state followed by an imbalance between T-helper and T-suppressor cells and the susceptibility or resistance of the β-cells to injury. Because some stress hormones (particularly cortisol) are known to modulate the immune system and others to alter islet β-cell activity (epinephrine, glucagon, cortisol), there has been speculation about the role of such modulation on the process of islet injury. Thus, neurohormonal changes associated with stress have been proposed as one of the environmental factors that interact with hereditary factors known to be associated with the risk of developing Type 1 diabetes.

Potential Role in the Etiology of Type 2 Diabetes Mellitus
Studies have suggested a possibility that a glucose-sensing defect may be the explanation for some of the abnormal neuroendocrine findings in this syndrome. The poor suppression of glucagon by glucose, the elevation of catecholamines unrelated to any ketoacidosis, and the supersensitivity to exercise induced increases in GH or its paradoxical increase by oral glucose in some individuals with mild hyperglycemia may be a part of the underlying disease.

Increased insulin release may be observed in Type 2 diabetes during the infusion of the α-adrenergic receptor blocking agent phentolamine, and this implies an increased α-adrenergic receptor activity in such subjects. Infusion of a synthetic somatostatin analog in dogs produces hyperglycemia and impairment of glucose-induced
insulin release similar to that found in Type 2 diabetes. A similar
effect has been observed with infusion of the neuropeptide galanin,
which is present in pancreatic nerves of some species.

A mouse model of diabetes and obesity (ob/ob) has been found
to be supersensitive to catecholamines and stress. It has been
suggested that this is a key factor in the development of diabetes in
this model.

Although none of these findings are conclusive, it is apparent that
activation of neuroendocrine systems that impair glucose sensitivity
of the islet β-cell can produce a syndrome quite similar to Type 2
diabetes.

Regardless of etiologic considerations, it is clear that stress hyper-
glycemia in such patients is almost certain to be more severe and
to be less well counteracted than in normal subjects. This will have
important therapeutic implications.1

CLINICAL MANAGEMENT OF STRESS-INDUCED HYPERGLYCEMIA

Normal Subjects

The treatment of stress hyperglycemia resolves itself into three
separate approaches:1

1. Maintenance of the hyperglycemia for those conditions in which
there is a real or potential deficiency of CNS uptake that can be
reversed by maintaining or even increasing the hyperglycemia.
   • These include hypovolemic and hypotensive states, in patients
     with cerebrovascular occlusive disease or with MI and low
     cardiac output or in hypoxic states.

2. Increasing glucose turnover by administering glucose and insulin
   or insulin alone for those conditions in which an increase of
   glucose use by insulin sensitive tissues is desired such as in burns,
   trauma or cold stress.

3. No treatment in those conditions in which there is no change of
   nutrient need. If hyperglycemia becomes severe, it can be treated
   with insulin alone, because the extra glucose being produced is
   not providing any needed function.
   • This occurs in most pain related syndromes, particularly those
     in which significant amounts of trauma have not occurred and
     there is no need for increased glucose use or nutrient support
     for injured tissues. A similar situation occurs in hypothermia
     in which total body metabolism is reduced. In the absence
     of extra glucose administration, hyperglycemia is unusual.
     However, if glucose is given to hypothermic humans, rather
     severe hyperglycemia can occur. Usually, all that is necessary
     is to stop the administration of exogenous glucose.

Type 1 Diabetes Mellitus Patients

Stress hyperglycemia in the diabetic patient has the same implications
as it does in the normal population.

In burns, trauma, MI or surgery related to trauma or in which
traumatic injury is likely to be extensive, the need for increased
nutrient delivery to peripheral tissues, in a Type 1 diabetic patient
is similar to that in normal subjects. Again, the need for increased
substrate use may be severe and although euglycemia may be
achieved by reducing caloric intake, this is not the desirable
treatment. As in the normal individual, carbohydrate, fat and protein
either orally or intravenously should be given along with sufficient
additional insulin to maintain euglycemic levels. In order to suppress
hepatic glucose production, it may be necessary to administer large
amounts of intravenous carbohydrate. If hyperglycemia occurs,
then additional insulin should be given along with the additional
carbohydrate rather than restricting carbohydrate calories, because
the goal is to promote nitrogen uptake in injured tissues while
sparing protein resources from gluconeogenesis.

In trying to anticipate insulin need during surgical procedures, a
number of approaches have been taken. In general terms, insulin should
be administered as a basal amount plus an amount in proportion to
expected caloric intake. In uncomplicated surgical procedures, long
acting insulin may be reduced to approximately 50% of the usual dose
and additional caloric need may be covered by monitoring plasma
glucose before and after the surgery. Plasma glucose levels are to be
maintained between 150 mg/dL and 200 mg/dL.

Under complex surgical conditions, long-acting insulins have not
been used and the patients have been switched to 6 hourly injections
of subcutaneous regular insulin or to continuous intravenous insulin
infusion along with sufficient carbohydrate to provide at least 600
calories per 24 hours, preferably 1,000 calories or more per 24 hours.
Insulin dosage must be individualized because insulin sensitivity
varies considerably between the patients. Because counter-
regulatory hormones are suppressed by many anesthetics, it may be
the postoperative phase in which insulin resistance will be most
severe.

Normal prehepatic basal insulin secretory rates for a lean
individual are approximately 15–25 U/d in the basal state. One can
estimate insulin need on the basis of this requirement. Approximately
an equal amount of insulin appears to be required to maintain
normal glucose homeostasis during the provision of a 2,000 to 2,500
calorie diet. These considerations can lead to rough estimates of
insulin need in lean Type 1 diabetic patients to be 40–50 U/d.

The major problem in Type 1 diabetes is the inability to anticipate
the impact of neuroendocrine control mechanisms upon plasma
glucose. It is clear that stress produces increased glucose levels and
a tendency towards ketosis in poorly controlled Type 1 diabetic
patients.

The recognition of hypoglycemia-associated autonomic failure
has revealed that autonomic counter-regulation may be expected to
vary from day to day in some patients. Thus, autonomic excess and/
or deficiency may be quite common and contribute significantly to
hypo- and hyperglycemia.

Type 2 Diabetes Mellitus Patients

In Type 2 diabetes, the usual regulatory mechanisms for maintaining
a constant plasma glucose level remain intact although impaired.
That is, insulin secretion is still present and it responds to glucose.
The sensitivity of this response is reduced, and therefore, any
nutrient challenge or challenge from an increased output of counter-
regulatory hormones will result in greater degrees of hyperglycemia
for longer periods of time. However, as in the normal individual,
these mechanisms will tend to stabilize plasma glucose levels even
during stress. Thus, with the mild forms of stress, the reregulated
plasma glucose level will tend to remain constant. This level is greater
than the normal population.

Presumably, the glucose sensitivity of the islets will depend on
the degree of hyperglycemia prior to the stressful event. Individuals
under relatively poor control will, therefore, be expected to become
much worse and perhaps be unable to reregulate due to the increased
glycosuria. If so, volume depletion and increased stress hormone
responses will occur. This is presumably the explanation for the
development of ketoacidosis during sepsis, trauma and surgical
interventions in relatively poorly controlled Type 2 diabetic patients.
The major treatment decision that must be made in the Type 2
diabetic patient is whether or not to stop an oral agent and to
institute insulin treatment. Well-controlled patients will manage
quite well during elective surgery and other minor stressful
situations. However, in any poorly controlled patient during episodes
of bacterial sepsis, MI, burn major trauma, and so on, the stress
response may overwhelm the islet. In this case, insulin treatment
must be instituted.1
Section 5

Diabetology

STRESS HYPERGLYCEMIA AND UNDIAGNOSED DIABETES IN THE HOSPITAL SETTING

The number of hospital in-patients with diabetes has increased and is rising inexorably. In addition to those with diagnosed diabetes, there are two other groups of patients with hyperglycemia in hospital. First, there are those with unrecognized diabetes occurring during hospitalization and subsequently confirmed after discharge and, secondly, those with so-called “hospital-related” hyperglycemia or stress hyperglycemia (fasting plasma glucose > 126 mg/dL (7 mmol/L) or random > 198 mg/dL (11 mmol/L), occurring during hospitalization, which reverts to normal after discharge. When the burden of “in-hospital hyperglycemia” is considered to include all three groups, then the prevalence is approximately 40% of all hospital in-patients.

Benefit of Blood Sugar Control in In-Hospital Hyperglycemia

There is compelling evidence that poorly controlled blood glucose (BG) levels are associated with a higher in-hospital morbidity and mortality, prolonged length of stay, unfavorable postdischarge outcomes and significant excess health care costs. Umpierrez et al. (2002) showed that patients with new hyperglycemia had an 18-fold increased in-hospital mortality and patients with known diabetes had a 2.7-fold increased in-hospital mortality when compared with normoglycemic patients. A joint position statement from the American College of Endocrinology (ACE) and the American Association of Clinical Endocrinologists (AACE) on inpatient diabetes and metabolic control concluded that hyperglycemia in hospitalized patients is a common, serious and costly health care problem. There was a strong recommendation for early detection of hyperglycemia and an aggressive management approach to improve outcomes.

ACUTE CORONARY SYNDROMES

In the management of MI, a meta-analysis of 15 studies showed that BG greater than 120 mg/dL (6.1 mmol/L), with or without a prior diagnosis of diabetes, was associated with an increased in-hospital mortality and subsequent heart failure. Current evidence supports the use of intravenous insulin in the first 24 hours and intensified subcutaneous insulin for 3 months in the setting of ST-segment elevation myocardial infarction (STEMI) where the diabetes and insulin-glucose infusion in acute myocardial infarction (DIGAMI) 1 study (1997) showed a 29% reduction in mortality at 1 year. Other randomized controlled trials such as DIGAMI 2 (2005) and CREATE-ECLA have failed to reproduce these findings.

Observational data from the UK, Myocardial Ischaemia National Audit Project (MINAP) of patients with troponin-positive acute coronary syndrome (ACS) demonstrated poorer outcomes in those with an elevated BG on admission, with 30-day mortality of 20.2% in those with BG greater than 170 mg/dL (9.4 mmol/L). Of 38,864 patients recorded on the MINAP database, around 10% (of those with no prior diagnosis of diabetes) had an admission BG greater than 250 mg/dL (14 mmol/L). Patients who did not receive treatment with intravenous insulin had a relative increased risk of death of 56% at 7 days and 51% at 30 days.

Stress hyperglycemia and established diabetes have similarly increased mortality from acute myocardial infarction (AMI). In a New York municipal hospital cohort of patients with AMI, 3-year mortality was 52% in those with stress hyperglycemia (defined as admission BG > 7.0 mmol/L) compared with 42% in those with diabetes. The 3-year death rate in those with normal glucose levels was 24% in the same study.

In the DIGAMI study, the effect of reasonable glycemic management (BG < 10 mmol/L) for those with no prior insulin therapy and stratified as having low coronary risk factors produced a 52% improvement in mortality. This group would have included those with stress hyperglycemia.

Estimates of the incidence of stress hyperglycemia at presentation of AMI range 10–16%. This compares with estimates of prevalence of diabetes at presentation of AMI of 25–32%.

Good clinical practice demands measurement of plasma glucose on diagnosis of an ACS. Hyperglycemia indicates a need for rapid control in the acute situation when the first few hours are critical.

ACUTE STROKE

The prevalence of previously diagnosed diabetes in patients with acute stroke is 8–28% but an additional 6–42% have unrecognized pre-existing dysglycemia. Plasma glucose at presentation is a major prognostic factor. One series of 86 patients with acute stroke demonstrated that full functional recovery at 4 weeks was restricted to those with presenting BG levels less than 8 mmol/L. None of the individuals with a raised presenting plasma glucose regained full function by 4 weeks. The extent to which this reflects the metabolic stress response in proportion to the severity of the cerebrovascular insult as opposed to hyperglycemia itself impairing subsequent recovery from ischemic damage cannot be ascertained from these observational data.

In a systematic review of observational studies examining the prognostic significance of hyperglycemia in acute stroke, the unadjusted relative risk of in-hospital or 30-day mortality was 3.07 (95% CI 2.50–3.79) in nondiabetic patients with admission plasma glucose level greater than 6–8 mmol/L and 1.30 (95% CI 1.04–1.63) in those with known diabetes. The relative risk of poor functional outcome in hyperglycemic nondiabetic patients was 1.41 (95% CI 1.16–1.73). It appears that sudden increase in plasma glucose levels impair tissue function more in those individuals who have not been habituated to hyperglycemia.

CARDIAC SURGERY

Most of the outcome data for patients undergoing cardiac surgery relates to the Portland Diabetic Project, which was a nonrandomized observational study of 5,510 patients undergoing cardiac surgery during 1987–2005. This has shown that patients with hyperglycemia managed with an intravenous infusion titrated to normoglycemia for 3 days postoperatively had improved mortality, reduction in deep sternal wound infections and reduction in length of stay.

CRITICAL CARE SETTING

The landmark study by Van den Berghe et al. (2001) showed that postoperative intensive insulin therapy (IIT) reduced mortality and morbidity in patients in the surgical intensive treatment unit (ITU). In a later study by the same group in medical ITU patients, IIT reduced morbidity but not mortality (2006). Randomized trials of IIT have shown inconsistent effects on mortality and increased rates of severe hypoglycemia. A recent meta-analysis 17 of 26 trials involving 13,567 patients including the recent NICE-SUGAR trial, the pooled relative risk of death with IIT compared with conventional therapy was 0.93 (95% CI 0.83–1.04). Fourteen trials reported hypoglycemic events and showed a significant increase in severe hypoglycemia with a relative rate (RR) of 6.8 (95% CI 4.5–9.0). The different targets of IIT did not influence either mortality or risk of hypoglycemia.

In-Hospital Glycemic Control Targets: Recommendations

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
• A target of >180 mg/dL (10 mmol/L) or <110 mg/dL (6.1 mmol/L) is not recommended.

Merits of Intravenous Insulin Therapy
The mechanisms behind the improved outcomes from intravenous insulin are numerous. The vasodilatory, anti-inflammatory and antithrombotic effects of insulin have been studied. In vitro, insulin induces a dose-dependent increase in nitrous oxide synthase production in the endothelium. Ultimately, insulin treatment may improve endothelial function in patients with diabetes.

CONCLUSION
Neural regulation of pancreatic islet in conjunction with other hormonal glucoregulatory systems is an important component of plasma glucose regulation, which contributes significantly to the normal disposition of exogenous nutrients and to defining the glycemic response to environmental stress. The neuroendocrine system tends to modulate the intrinsic regulatory control system for plasma glucose, which involves the liver, peripheral tissues and islet as the primary nutrient and substrate sensors. The sensitivity and function of all three elements of this system are responsive to neuroendocrine control.

Stress responses that occur in normal animals or humans may or may not be beneficial for long-term survival. Thus, evaluation of the impact of the hyperglycemia found under such circumstances must be made prior to a treatment decision.

However, there are many circumstances under which hyperglycemia may be beneficial or even essential for survival. Treatment will depend on which category of hyperglycemic response one can place the particular patient into.

Treatment considerations vary from patient to patient and depend upon the nature of the stress and the specific response to that stress in the individual case.

In DM, neuroendocrine abnormalities are common. At times, a pathophysiologic separation of stress hyperglycemia and Type 2 diabetes is not possible. Both involve alterations of the regulation of hepatic glucose output and peripheral sensitivity of tissues to insulin, as well as alterations of islet function. Therefore, regardless of etiologic significance, neuroendocrine control systems must be taken into account in the diagnosis, evaluation and treatment of any hyperglycemic state in humans.1

Type 2 DM frequently presents for the first time at hospitalization for acute illness. This presentation is complicated by stress hyperglycemia resulting from the catecholamine and cortisol elevations. Although this may cause problems when one wants to evaluate an effect of diabetes per se, from the perspective of the patient with a life-threatening condition exacerbated by dysglycemia, exact definitions of diabetes are not relevant at the acute setting and management of hyperglycemia is essential in improving the outcome.

REFERENCES