Stress Hyperglycemia

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STRESS HYPERGLYCEMIA-A TRANSIENT PHENOMENON[1]

A high proportion of patients suffering an acute stress such as stroke or myocardial infarction may develop hyperglycemia, even in the absence of a preexisting diagnosis of diabetes.

Both human and animal studies suggest that this is not a benign occurrence and that stress-induced hyperglycemia is associated with a high risk of mortality after both stroke and myocardial infarction.

Moreover, recent evidence that glucose lowering with insulin reduces ischemic brain damage in animal models of stroke suggests that stress-induced hyperglycemia may be a modifiable risk factor for brain damage.

Despite these observations, the relationship between glucose levels and outcome after stroke in diabetic and non-diabetic patients has not been well characterized, and those studies that have examined this relationship have reported conflicting results.

So it is important to analyze available studies about stress hyperglycemia. I therefore systematically reviewed the published literature to summarize the available evidence and to estimate the strength of the association between admission hyperglycemia and both short-term mortality and functional recovery after stroke.

DEFINITION

Elevated blood glucose in presence of normal HbA1c, regardless of diabetes status, may therefore represent a stress response

A random glucose level drawn on admission 108-180mg/Dl (or)

Fasting glucose level the morning after admission 110-141 mg/dL

Hypothalamic-pituitary-adrenal axis is integral to this neuroendocrine stress response.

Stress hyperglycemia is believed to trigger sympatho-adrenal tone, increased stress hormones such as cortisol and noradrenaline, or damage to central autonomic control sites.

PREVALENCE

- One-third of all individuals with hyperglycemia admitted to the hospital do not have a previous diagnosis of diabetes
- Hyperglycemia is present in 20 to 40% of patients with acute ischemic stroke, regardless of a history of diabetes mellitus
- Hyperglycemia is a risk factor for adverse outcomes during acute illness, surgery or steroid treatment.

STUDIES ON STRESS HYPERGLYCEMIA

The definition of stress hyperglycemia also varied among studies. Most studies did not specify whether whole blood or plasma glucose was measured. Of those that did specify, one study measured whole blood glucose, and the rest measured plasma glucose levels. A random glucose level drawn on admission was used to define stress hyperglycemia in 10 of the 32 studies (with cutoffs ranging from 6 to 10 mmol/L [108 to 180 mg/dL]). Another nine studies based the definition of stress hyperglycemia on fasting glucose level the morning after admission (ranging from 6.1 to 7.8 mmol/L [110 to 141 mg/dL]). Two of the 32 studies did not specify whether the glucose level used to define stress hyperglycemia in individual patients was random or fasting. The remaining 11 of 32 studies did not identify the glucose cutoffs used to define stress hyperglycemia; these studies reported either the mean glucose level in patients with good versus poor outcomes or the relationship between outcomes and glucose as a continuous variable on regression analysis.

INCREASED RISK?

Several explanations may account for the observed association between hyperglycemia and poor prognosis after ischemic stroke. **First,** hyperglycemia may be directly toxic to the ischemic brain. Although the mechanism is not fully understood, accumulation of lactate and intracellular acidosis in the ischemic brain (produced through anaerobic cerebral glucose metabolism) may contribute.

Second, hyperglycemic patients are relatively deficient in insulin. This leads to both reduced peripheral uptake of glucose (increasing the amount of glucose available to diffuse into brain) and increased circulating free fatty acids. Free fatty acids may impair endothelium-dependent vasodilation and, in hyperglycemic patients with acute myocardial infarction, have been shown to promote calcium overload and arrhythmias; however, the effect

of excessive circulating free fatty acids on ischemic brain has not been studied.

Third, patients without a diagnosis of diabetes who develop stress hyperglycemia are likely to have dysglycemia (i.e., blood glucose level above the normal range but below the threshold for diabetes) or undiagnosed diabetes when not stressed. Patients with dysglycemia or undiagnosed diabetes have a higher risk of vascular disease than patients with normal blood glucose level. These patients could sustain more ischemic damage at the time of infarction as a result of more extensive underlying cerebral vasculopathy compared with those who do not develop stress hyperglycemia. Although the extent of cerebral atherosclerosis in patients with and without stress hyperglycemia has not been studied, hyperglycemia may be an important determinant of the widespread changes in both small cerebral blood vessels and large extracranial vessels seen in diabetic patients. Furthermore, even nondiabetic-range hyperglycemia is associated with endothelial dysfunction, another potential mechanism of cerebrovascular disease in these patients. Patients with dysglycemia or undiagnosed diabetes may also have a higher risk of cardiac events after stroke; however, the available evidence suggests that most of the excess mortality in patients with stress hyperglycemia is due to the neurological effect of the large stroke and not to a higher fatal cardiac event rate.

Fourth, hyperglycemia may disrupt the blood-brain barrier and promote hemorrhagic infarct conversion. Consistent with this possibility is the observation that in 138 diabetic and nondiabetic patients with ischemic stroke treated with intravenous recombinant tissue plasminogen activator, higher admission serum glucose level was associated with a higher risk of hemorrhagic conversion of the infarct, with a substantial increase in risk with levels >8.4 mmol/L. This study did not report mortality or functional recovery from stroke in relation to admission glucose level and therefore was not included in this overview. Only one study included in the overview reported the risk of hemorrhagic infarct conversion in relation to glucose level. This study followed 1259 patients with ischemic stroke randomized to a low-molecular-weight heparinoid versus placebo; in the two groups combined, there was no association between admission glucose level and risk of hemorrhagic infarct conversion. The reason for the discrepancy between these two studies is not clear.

Fifth, stress hyperglycemia may be a marker of the extent of ischemic damage in patients with stroke. For example, patients with severe or fatal strokes might develop hyperglycemia because of greater release of "stress hormones" such as cortisol and norepinephrine. Indeed, a logistic regression analysis of data from 345 patients with stroke showed that the strength of the positive association between hyperglycemia and mortality lessened after accounting for the severity of stroke (as indicated by decreased level of consciousness and weakness score at the onset of stroke). However, animal studies showing that administration of insulin reduces the size of the infarct and improves prognosis after stroke strongly support the view that stress hyperglycemia is of pathophysiological significance in patients with stroke and is not simply an epiphenomenon of the stress response to stroke.

Stress hyperglycaemia is a predictor of abnormal glucose tolerance in Indian patients with acute myocardial infarction.[2]

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66 non-diabetic Indian patients with acute myocardial infarction were assessed prospectively for the presence of hyperglycaemia and the value of this admission hyperglycaemia and glycosylated haemoglobin (HbA1) levels in reflecting the glucose tolerance status of the patients was studied. Hyperglycaemia, defined as admission plasma glucose greater than or equal to 8 mmol/l was detected in 49% of the patients, whilst raised HbA1 values were seen in 11%. The admission plasma glucose (APG) correlated significantly with both the HbA1 levels and with the 2 hour glucose value in the oral glucose tolerance test (p less than 0.001). An oral glucose tolerance test performed 3 months after the acute episode revealed that 35 patients (53%) had abnormal glucose tolerance according to WHO criteria. Of the patients with initial hyperglycaemia, 75% had abnormal glucose tolerance tests, whilst 32% of patients with normal APG had abnormal glucose tolerance. Abnormal glucose tolerance was also detected in all patients with raised HbA1 values (greater than 8.9%) and in 48% of patients with normal levels. The sensitivity and specificity of APG greater than or equal to 8 mmol/l for abnormal glucose tolerance was 68.6% and 74.2% respectively and that of raised HbA1 values were 20% and 100%. Hence an APG greater than or equal to 8 mmol/l in patients with myocardial infarction is more likely to indicate the presence of unrecognized abnormal glucose tolerance rather than stress. HbA1 measurements do not appear to offer any further advantage in the assessment of hyperglycaemia following myocardial infarction.

Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview.[3]

High blood glucose concentration may increase risk of death and poor outcome after acute myocardial infarction. We did a systematic review and meta-analysis to assess the risk of in-hospital mortality or congestive heart failure after myocardial infarction in patients with and without diabetes who had stress hyperglycaemia on admission.

Patients without diabetes who had glucose concentrations more than or equal to range 6.1-8.0 mmol/L had a 3.9-fold (95% CI 2.9-5.4) higher risk of death than patients without diabetes.

Adverse Effects of stress hyperglycemia.[4]

Hyperglycemia has a proinflammatory action that is normally rest rained by the anti-inflammatory effect of insulin secreted in response to stimulus

Acute stress hyperglycemia induced by glucose clamping in normal subjects and lasting 5 hours determines a significant increase of IL-6, IL-18 and tumor necrosis factor [alpha] (TNF-[alpha]) circulating levels.

So an increased oxidative stress may be a likely mechanism linking stress hyperglycemia to cardio vascular diseases.

An increased inflammatory immune process seems a likely mechanism linking acute hyperglycemia to poor cardiac outcome in MI patients.

Stress hyperglycemia has been associated with increased mortality in patients with myocardial infarction (MI).

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During MI, hyperglycemia is associated with increased levels of inflammatory markers, enhanced expression of cytotoxic T-cells, and reduced expression of T-cells, which are implicated in limiting the immune process

Oxidative stress caused by hyperglycemia occurs before the complication of diabetes become clinically evident.

Protein glycation glucose toxicity (depends upon ROS).

Recent research indicates hyperglycemia activates several major well characterized biochemical pathways leading to complications. (Diabetes vol. 52; Jan. 2003).

TREATMENT

The Glucose Insulin in Stroke Trial (GIST)

Glucose Potassium Insulin Infusions in the Treatment of Acute Stroke Patients with Mild to Moderate Hyperglycemia[6]

Hyperglycemia following acute stroke is strongly associated with subsequent mortality and impaired neurological recovery, but it is unknown whether maintenance of euglycemia in the acute phase improves prognosis.

In an explanatory, randomized, controlled trial to test safety, 53 acute (within 24 hours of ictus) stroke patients with mild to moderate hyperglycemia (plasma glucose between 7.0 and 17.0 mmol/L) were randomized to receive either a 24-hour infusion of 0.9% (154 mmol/L) saline or a glucose potassium insulin (GKI) infusion at 100 mL/h. The GKI consisted of 16 U human soluble insulin and 20 mmol potassium chloride in 500 mL 10% glucose. Blood glucose was measured every 2 hours with Boehringer Mannheim Glycaemic test strips, pulse and blood pressure were measured every 4 hours, and plasma glucose samples were taken every 8 hours. Insulin concentration in the GKI was altered according to BM glucose values

There were no statistically significant differences between the two groups at baseline. Twenty-five patients received GKI, one of whom required intravenous glucose for symptomatic hypoglycemia. Plasma glucose levels were nonsignificantly lower in the GKI group throughout the infusion period. Four-week mortality in the GKI group was 7 (28%), compared with 8 (32%) in the control group.

Treatment of even trivial hyperglycemia during acute illness is fundamental to improve survival. Because insulin is the best choice to normalize glucose during stress, accepting the premise will inevitably bring increased insulin use in ICUs

Procedure for Hospital Management of Newly Identified Hyperglycemia

A follow up plasma glucose measurement should be obtained, or bedside capillary blood glucose monitoring should be done. If hyperglycemia persists, the patient and primary care physician should be informed.

Controlling Hyperglycemia in the Hospital: A Matter of Life and Death[7]

Six million US hospitalizations per year are accompanied by hyperglycemia. The degree of hyperglycemia may be an important predictor of morbidity and mortality among patients with myocardial infarction or stroke and those undergoing surgical procedures, including coronary artery bypass. Hyperglycemia should be aggressively controlled from the time of admission regardless of patients' primary medical problem or previous diabetes status. New methodologies for identifying, monitoring, and treating hyperglycemia are needed.

The data on the importance of controlling glucose in hospital settings spans diverse disciplines of medicine. Studies in the areas of stroke, myocardial infarction (MI), bypass surgery, and wound and nosocomial infections all point to the tremendous potential to reduce morbidity and mortality among hospitalized patients with hyperglycemia.

It is essential to identify hyperglycemia at the time of hospital admission and to implement therapy to achieve and maintain glucose levels as close to normal as possible, regardless of a patient's primary reason for admission or previous diabetes status.

Is hyperglycemia caused by stress or diabetes? It doesn't matter

Among hospitalized patients with acute MI, an admission glucose value of >180 mg/dl predicted undiagnosed diabetes rather than stress hyperglycemia in a study in which newly recognized hyperglycemic individuals had subsequent glucose tolerance testing performed 2 months after hospital discharge.[4,5] The Diabetes Insulin-Glucose in Acute Myocardial Infarction (DIGAMI) trial demonstrated significant reductions in mortality when an intensive insulin regimen was administered to hyperglycemic patients hospitalized with acute MI.[4,5] Enrollment in the DIGAMI study included all patients with glucose values >198 mg/dl without regard to previous diabetes status. Nearly 15% of the study population did not have a history of glucose intolerance.

Intravenous insulin makes physicians uncomfortable

Studies demonstrate the importance of controlling glucose and the advantages of intravenous insulin over subcutaneous insulin. Many physicians are uncomfortable treating diabetes, and the use of intravenous insulin therapy has been limited to intensive care units or special care units in which the nursing staff has expertise using intravenous insulin infusions.[7]

New technology is near

As continuous subcutaneous glucose monitoring is now becoming available, monitoring of glucose and treatment of hyperglycemia may become much easier. This type of monitoring device measures interstitial glucose every 5 minutes.

FUTURE RISK

Patient has an increased risk of diabetes in the future. Control with intensive insulin therapy during acute illness helps in better control.

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