# EFFECT OF HYPERGLYCEMIA ON STROKE OUTCOMES

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## ABSTRACT

***Objective:*** To review published data about the relationship between hyperglycemia and the outcome of patients with stroke.

***Results:*** Stroke is the most frequent cause of permanent disability in the Western world and the third leading cause of death among Americans. Each year, more than 500,000 Americans have a cerebrovascular accident. In the medical literature, numerous reports have discussed how hyperglycemia during acute stroke, regardless of a patient's prior diabetes status, has been associated with significantly higher morbidity, higher mortality, longer hospital stays, reduced long-term recovery, and diminished ability to return to work. In the United States alone, an estimated $300 million in additional health-care costs are incurred among hospitalized patients with stroke who also have high blood glucose levels. Treatment of hyperglycemia has safely, successfully, and effectively yielded glucose levels in the normal range in the hospital setting under the direction of specialty physicians and should be implemented in patients with stroke.

***Conclusion:*** Until convincing randomized prospective trials prove that tight glycemic control does *not* improve stroke outcomes, the overwhelming preponderance of data suggests that aggressive glucose management should be the standard care in all patients with stroke and hyperglycemia. **(Endocr Pract. 2004;10[Suppl 2]:34-39)**


**Abbreviations:**
CI = confidence interval; GIST = Glucose Insulin in Stroke Trial; RR = relative risk

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## BACKGROUND

Stroke is the third leading cause of death among Americans and is the most frequent cause of permanent disability in the Western world (1-3). Each year, more than 500,000 Americans have a cerebrovascular accident. During the past 3 decades, many large cohort and retrospective analyses have demonstrated not only an increased risk of fatal and nonfatal stroke among persons with diabetes but also a directly related adverse effect of the degree of hyperglycemia at the time of hospital admission on stroke outcomes and related disability.

Beginning more than 3 decades ago, various investigations including the Framingham Study (4), the Paris Prospective Study (5), the Whitehall Study (6), the Multiple Risk Factor Intervention Trial (7), and the Rancho Bernardo Study (8) demonstrated that the risk for stroke was dramatically higher among patients with diabetes than among those without diabetes. For example, the Rancho Bernardo Study 12-year mortality data showed that enrolled men 35 to 57 years old with diabetes had a relative risk (RR) of 2.8 (95% confidence interval [CI], 2.0 to 3.7) for stroke-related mortality in comparison with men without diabetes after adjustments were made for age, race, income, and cardiovascular risk factors (8).

Similarly, Palumbo et al (9) reported that transient ischemic attacks were 3 times more likely in patients with diabetes than in those without diabetes, and the risk of stroke was almost twice as great in patients with diabetes. Kannel and McGee (10) reported a difference in stroke outcomes between men and women with and those without diabetes; the risk of stroke among women with diabetes was 3.6 times higher than among those women without diabetes, and it was 2.5 times greater in men with diabetes than in those without diabetes.

## STROKE RISK IN PATIENTS WITH HYPERGLYCEMIA BUT NOT DIABETES

The collection of data on increased risk for cardiovascular disease and stroke among patients with hyperglycemia, who did not have diabetes before their event, also dates back several decades. The Whitehall Study (6) reported a mortality rate of 12 per 1,000 person-years for

patients without diabetes, 40 per 1,000 person-years for those with undiagnosed diabetes, and 27 per 1,000 person-years for patients with diagnosed diabetes. The Paris Prospective Study (5) demonstrated comparable findings; the mortality rate was 23% among patients with undiagnosed diabetes, 20% among those with a definitive diagnosis of diabetes, and 9% among those without diabetes.

More recently, Williams et al (11) reported that hyperglycemia was present in 40% of all hospital admissions for patients with stroke. Other studies that have specifically evaluated the prevalence of stroke accompanied by hyperglycemia among patients without a prior history of diabetes have found that from 12 to 53% of patients presenting with acute stroke have concomitant hyperglycemia (12-16).

These reported prevalences of hyperglycemia among patients with stroke parallel the findings described by both Levetan et al (17) and Umpierrez et al (18), who reported that a third of all hospitalized patients with hyperglycemia had no prior history of diabetes. Both investigative groups found that patients with newly discovered hyperglycemia had a significantly higher in-hospital mortality rate and a worse functional outcome than did patients with a prior history of diabetes and those with euglycemia.

In the report by Umpierrez et al (18), patients with hyperglycemia had a dramatically higher in-hospital mortality rate (16%) than did those with diabetes (3%). Similar to this information, Levetan et al (19) found the mortality rate at 1 month to be 12% among hospitalized patients with hyperglycemia without a previous diagnosis of diabetes.

## HYPERGLYCEMIA: EPIPHENOMENON OR INDEPENDENT RISK FACTOR?

Considerable debate exists about whether high blood glucose levels during acute stroke are simply a reflection of the stress response to the degree of stroke severity. Many studies have correlated stroke outcome with the degree of hyperglycemia. Although van Kooten et al (12) noted a clear association between blood glucose levels at the time of hospital admission and stroke outcome, they found no significant correlation between glucose and catecholamine levels.

Recent studies have also found that administration of insulin in animal models with acute stroke both reduced the size of the infarct and improved the prognosis (20,21). In light of the equally high (if not higher) mortality rates among patients with hyperglycemia in comparison with those with diagnosed diabetes, patients without a history of diabetes should perhaps be managed more aggressively. Typically, both groups are left untreated or treated only with sliding-scale coverage.

## RELATIONSHIP BETWEEN STRESS AND GLUCOSE—NOT WHAT YOU THINK

An admission blood glucose value in excess of 180 mg/dL was more predictive of undiagnosed diabetes than stress-induced hyperglycemia among a group of hospitalized patients with newly recognized hyperglycemia who underwent follow-up glucose tolerance testing 2 months after dismissal from the hospital (22). No unique diagnostic criteria have been established for making a diagnosis of diabetes in the stressed state. Thus, all patients identified with either two fasting blood glucose levels of more than 125 mg/dL or random blood glucose values in excess of 199 mg/dL on two occasions fulfill the diagnostic criteria for diabetes (23).

Stress-related hyperglycemia has eluded consistent documentation. Many reports have found that stress has no significant effect on glucose regulation, whereas other studies have found that stress results in diminished blood glucose values (24-33). A controlled study, in which a glucose-insulin infusion system was used among patients with diabetes, found that the glucose response to an active stressor was idiosyncratic (23). Only half of these study subjects demonstrated any degree of increase in blood glucose level, ranging from 20 to 30 mg/dL, in response to stress (23). The effect of surgical intervention on blood glucose levels has also been evaluated in the diabetic population; even major surgical procedures were associated with a mean increase in glucose of only 37 mg/dL (34).

## HYPERGLYCEMIA WITHOUT A DIABETES HISTORY AND STROKE

In an extensive meta-analysis by Capes et al (35), evaluation of 32 studies revealed that both ischemic and hemorrhagic stroke had an in-hospital or 30-day mortality with a RR of 3.07 (95% CI, 2.5 to 3.79) when admission glucose levels were more than 108 to 144 mg/dL (6 to 8 mmol/L). Admission glucose level also predicted poorer functional recovery among those patients without a prior history of diabetes (RR, 1.41; 95% CI, 1.16 to 1.73). Jorgensen et al (36) reported that among 623 patients with hyperglycemia who did not have a history of diabetes, mortality and initial stroke severity increased linearly with increasing admission glucose values beyond 108 mg/dL.

The prevalence of unrecognized diabetes remains extremely high. By age 65 years, 20% of the population has diabetes, yet more than a third of the cases remain undiagnosed (37). Because of the mean age of patients with stroke, the likelihood is high that hyperglycemia in such patients may represent unrecognized diabetes.

Regardless of the cause, persistent hyperglycemia leads to more extensive cerebral vasculopathy and

endothelial dysfunction and should not be dismissed and left untreated in patients with stroke. Relative to this point, Riddle and Hart (16) found that 21 of 40 patients with stroke without a previous history of diabetes (53%) had hemoglobin A1c values of more than 10%. Hyperglycemia without a history of diabetes is also a risk factor for transient ischemic attacks (9).

## DIABETES AND ACUTE STROKE

Epidemiologic data have demonstrated an increased risk of stroke among patients with diabetes. The Framingham Study (4) found that the incidence of stroke was 2.5 times higher in men with diabetes and 3.6 times higher in women with diabetes than in their respective counterparts without diabetes. Several studies have suggested that hyperglycemia is an independent risk factor influencing the severity of stroke.

In a prospective analysis, Pulsinelli et al (15) reported that both patients with diabetes and those with hyperglycemia without an established diagnosis of diabetes had worse neurologic outcomes than did those who were normoglycemic. Stroke-related deficits were more severe when the admission glucose values were more than 120 mg/dL (6.7 mmol/L). Only 43% of the patients with an admission glucose value of more than 120 mg/dL were able to return to work, whereas 76% of patients with lower glucose values regained employment.

Jorgensen et al (36) evaluated the relationship between plasma glucose level and mortality rate among 233 patients with diabetes who were hospitalized with an acute stroke. Diabetes was an independent risk factor that doubled the mortality rate. Weir et al (38) found that a plasma glucose level in excess of 144 mg/dL within the first 24 hours after hospital admission was a risk factor independent of age, stroke type, and stroke severity, and it predicted a doubled mortality risk. Similarly, Asplund et al (39) demonstrated that the presence of diabetes adversely affected short- and long-term neurologic outcomes among patients with both ischemic and hemorrhagic strokes.

In 2003, Baird et al (40) reported that persistent hyperglycemia throughout hospitalization is an independent determinant of infarct expansion and is associated with worse functional outcome. Additionally, Alvarez-Sabin et al (41) recently reported that blood glucose levels exceeding 140 mg/dL are an independent predictor of poor outcome and functional dependence at 3 months among patients with stroke undergoing intravenous reperfusion with tissue plasminogen activator.

Other studies have found that admission blood glucose levels or hemoglobin A1c values (or both) correlate with stroke size, clinical severity, and prognosis (42-59). Although many studies suggest that normalization of glucose values may improve stroke outcomes among patients with diabetes and hyperglycemia (similar to the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction [DIGAMI] study), such studies have not been completed among patients with stroke (60). Scott et al (61) are conducting the first randomized trial among patients with stroke to determine the effect of isotonic saline versus insulin infusions among hospital admissions of patients with acute stroke and hyperglycemia (the Glucose Insulin in Stroke Trial [GIST]).

## HYPERGLYCEMIA AND HEMORRHAGIC STROKE

Several studies have demonstrated an increased association between hyperglycemia and transformation from an ischemic to a hemorrhagic stroke (62-64). Demchuk et al (62) found that hyperglycemia was the only independent risk predictor of intracerebral hemorrhage among 138 patients with ischemic stroke who received tissue plasminogen activator. Both diabetes and admission hyperglycemia in patients without diabetes are predictors of poor outcome after supratentorial intracranial hemorrhage.

## PATHOPHYSIOLOGIC FEATURES OF HYPERGLYCEMIA IN STROKE

Several mechanisms have been proposed to explain the relationship of hyperglycemia and poor prognosis after stroke. Experts generally agree (65-72) that an increase in plasma glucose level during stroke results in intracellular acidosis attributable to an increased substrate for anaerobic metabolism. The most consistent finding has been the correlation between hyperglycemia and acidosis occurring immediately after the onset of stroke. Acidosis and increases in lactate formation may worsen glial, neuronal, and cell membrane damage; increase free radical formation; and impair vasodilatation.

Investigators believe that hyperglycemia has a critical role in affecting the injured but still viable neurons, forcing them on to infarction rather than being salvaged. Additionally, hyperglycemia may contribute to the disruption of the blood-brain barrier (62,73,74). Furthermore, it may have a role in the conversion of ischemic to hemorrhagic strokes.

Published studies to date suggest that hyperglycemia itself has a pathologic role in worsening stroke outcomes. Data demonstrating that the extent of hyperglycemia does not correlate with catecholamine levels (along with insulin reducing infarct size) strongly suggest that hyperglycemia is not an epiphenomenon of stroke; rather, it is a marker of a patient with a dysglycemic diathesis, who should be considered at very high vascular risk.

In a retrospective review, Berger and Hakim (75) found that patients with hyperglycemia had substantially more cerebral edema with strokes. They identified this finding as a potential factor in worse clinical outcomes in comparison with those noted in normoglycemic patients with stroke.

## COSTS AND OUTCOMES

In general, hospitalized patients with hyperglycemia have longer hospital stays than do those with normoglycemia. Williams et al (11) found that 40% of their series of patients hospitalized with acute stroke had hyperglycemia. These patients had significantly more days in the hospital; thus, additional charges of nearly $1,500 per patient were accrued by patients with hyperglycemia in comparison with patients with normoglycemia. Extrapolating this to the 500,000 Americans hospitalized with stroke, of whom approximately 40% have glucose levels that are uncontrolled, nearly $300 million in additional health-care costs are attributable to hyperglycemia and diabetes.

Williams et al (11) also reported that almost all patients admitted to the hospital with stroke and hyperglycemia remained hyperglycemic, with mean blood glucose values exceeding 200 mg/dL throughout their hospital stay. Of these patients with hyperglycemia and stroke, 43% received no inpatient hypoglycemic drugs. Levetan et al (17) similarly found that 46% of such patients received no hypoglycemia medications.

A similar study (76), which focused only on patients with stroke, found a physician plan for further evaluation of diabetes in only 1% of patients (1 of 90) with hyperglycemia. Levetan et al (17) documented similar findings; among patients with hyperglycemia, almost no mention of hyperglycemia was evident in the progress notes. Furthermore, physicians did not document plans for obtaining follow-up glucose levels after admission in 95% of the cases.

Physicians are likely to assume that the hyperglycemia is a transient finding that results from the stress of acute illness, rather than consider the diagnosis of unrecognized diabetes. These studies demonstrate that physicians tend to overlook hyperglycemia, rather than understand, treat, and prevent the numerous complications that are associated with hyperglycemia and stroke outcomes.

## THE FUTURE

The GIST investigation (now under way) is comparing outcomes of patients with stroke and hyperglycemia treated with insulin versus saline alone (61). Preliminary data recently published from this study have shown that, among the first 53 patients entered in the study, the protocol was successfully implemented and safe.

## CONCLUSION

Data from many disciplines of medicine, including endocrinology with a focus on diabetes, indicate that improved outcomes are seen when acutely ill hospitalized patients are treated by a specialist rather than a generalist (77,78). It is now common knowledge backed by evidence-based medicine that patients hospitalized with acute myocardial infarction are significantly more likely to be alive at 12, 24, and 36 months after hospitalization when they have a specialist as their primary physician (60).

Insulin therapy has been clearly shown to be safe and efficacious. Until convincing data indicate that strict glycemic control does *not* improve stroke outcomes, the overwhelming preponderance of data suggests that tight glycemic control should be imperative among all patients with stroke, regardless of their diabetes history. The public and the entire health-care community should be aware of the increased risk for death and disability if hyperglycemia is not addressed immediately among hospitalized patients with stroke.

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